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REVIEW

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

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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

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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 V7171) 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, 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 (Hauss-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 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.

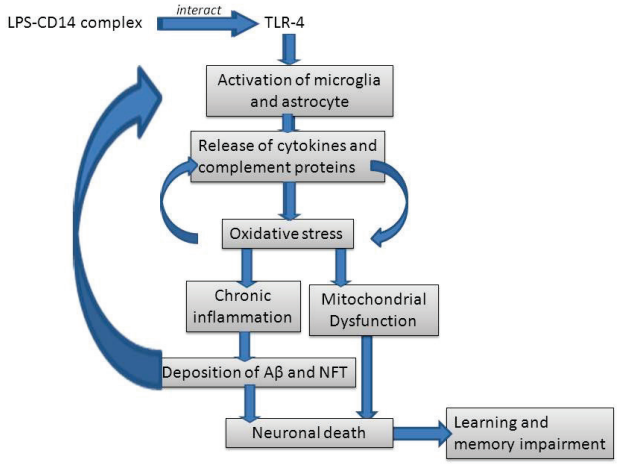

Fig. 1. Mechanism of LPS action in CNS.

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 O_2 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.*

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 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 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 for 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 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.

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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 (Behavior 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 *et al.* 1998
Young male and female Hooded Long Evans rats Adult male Albino Sprague Dawley 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 *et al.* 1998
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 (Y maze) and impaired spatial memory (Morris water maze)	Yamada *et al.* 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 *et al.* 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 *et al.* 2001
Adult male Wistar rats	250 µg/kg (i.p.)	Single injection	LPS impaired hippocampal-dependent spatial learning (Water maze)	Shaw *et al.* 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 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)	Fan *et al.* 2005

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 *et al.* 2006
Adult male Wistar rats	100 µg/kg (i.p.)	Single injection	LPS impaired recognition memory (Object recognition)	Hennigan *et al.* 2007
Adult male Wistar rats	5 mg/kg (i.p.)	Single injection	The behavioral 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 *et al.* 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 *et al.* 2014
Adult male Wistar rats	1 mg/kg (i.v.)	Single injection	LPS impaired cognitive performance (Barnes maze and inhibitory avoidance test)	Vasconcelos *et al.* 2014
Adult male Wistar rats	250 µg/kg (i.p.)	Single injection daily for 3 or 7 days	LPS for 7 days caused higher memory impairment compared to LPS for 3 days (Morris water maze)	Zhu *et al.* 2014
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 *et al.* 2015
Adult male Wistar rats	1 mg/kg (i.p.)	Single injection	LPS impaired passive avoidance memory retention	Anaeigoudari *et al.* 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 *et al.* 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 *et al.* 2016
Adult male Sprague Dawley rats	50 µg/5 µl (i.c.v.)	Single injection	LPS caused learning and memory impairment (Y maze and Morris water maze)	Song *et al.* 2016

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

References

ALZHEIMER'S DISEASE INTERNATIONAL: World Alzheimer Report. 2009.

ANAEIGOUDARI A, SHAFEI MN, SOUKHTANLOO M, SADEGHNIA HR, REISI P, BEHESHTI F, MOHEBBATI R, MOUSAVI SM, HOSSEINI M: Lipopolysaccharide-induced memory impairment in rats is preventable using 7-nitroindazole. *Arq Neuropsiquiatr* **73**: 784-790, 2015.

ANAEIGOUDARI A, SOUKHTANLOO M, REISI P, BEHESHTI F, HOSSEINI M: Inducible nitric oxide inhibitor aminoguanidine, ameliorates deleterious effects of lipopolysaccharide on memory and long term potentiation in rat. *Life Sci* **158**: 22-30, 2016.

BAKOS J, DUNCKO R, MAKATSORI A, PIRNIK Z, KISS A, JEZOVA D: Prenatal immune challenge affects growth, behavior, and brain dopamine in offspring. *Ann N Y Acad Sci* **1018**: 281-287, 2004.

BARDOU I, KAERCHER RM, BROTHERS HM, HOPP SC, ROYER S, WENK GL: Age and duration of inflammatory environment differentially affect then neuroimmune response and catecholaminergic neurons in the midbrain and brainstem. *Neurobiol Aging* **35**: 1065-1073, 2014.

BIVALACQUA TJ, SUSSAN TE, GEBSKA MA, STRONG TD, BERKOWITZ DE, BISWAL S, BURNETT AL, CHAMPION HC: Sildenafil inhibits superoxide formation and prevents endothelial dysfunction in a mouse model of secondhand smoke induced erectile dysfunction. *J Urol* **181**: 899-906, 2009.

BLASKO I, MARX F, STEINER E, HARTMANN T, GRUBECK-LOEBENSTEIN B: TNFalpha plus IFNgamma induce the production of Alzheimer beta-amyloid peptides and decrease the secretion of APPs. *FASEB J* **13**: 63-68, 1999.

BLATTEIS CM: Role of OVLT in the febrile responses to circulating pyrogens. *Prog Brain Res* **91**: 409-412, 1992.

BLOCK ML, HONG JS: Microglia and inflammation-mediated neurodegeneration: Multiple triggers with a common mechanism. *Prog Neurobiol* **76**: 77-98, 2005.

BOSSÙ P, CUTULI D, PALLADINO I, CAPORALI P, ANGELUCCI F, LARICCHIUTA D, GELFO F, DE BARTOLO P, CALTAGIRONE C, PETROSINI L: A single intraperitoneal injection of endotoxin in rats induces long-lasting modifications in behavior and brain protein levels of TNF-α and IL-18. *J Neuroinflam* **9**: 101, 2012.

BURTON MD, JOHNSON RW: Interleukin-6 trans-signaling in the senescent mouse brain is involved in infection-related deficits in contextual fear conditioning. *Brain Behav Immun* **26**: 732-738, 2012.

BUXBAUM JD, OISHI M, CHEN HI, PINKAS-KRAMARSKI R, JAFFE EA, GANDY SE, GREENGARD P: Cholinergic agonists and interleukin 1 regulate processing and secretion of the Alzheimer beta/A4 amyloid protein precursor. *Proc Natl Acad Sci U S A* **89**: 10075-10078, 1992.

CANDIRACCI M, PIATTI E, DOMINGUEZ-BARRAGÁN M, GARCÍA-ANTRÁS D, MORGADO B, RUANO D, GUTIÉRREZ JF, PARRADO J, CASTAÑO A: Anti-inflammatory activity of a honey flavonoid extract on lipopolysaccharide-activated N13 microglial cells. *J Agric Food Chem* **60**: 12304-12311, 2012.

CAVANAUGH SE, PIPPIN JJ, BARNARD ND: Animal models of Alzheimer disease: historical pitfalls and a path forward. *ALTEX* **1**: 279-302, 2014.

CHAI CK: The genetics of Alzheimer's disease. *Am J Alzheimers Dis Other Demen* **22**: 37-41, 2007.

CHARTIER-HARLIN MC, CRAWFORD F, HOULDEN H, WARREN A, HUGHES D, FIDANI L, GOATE A, ROSSOR M, ROQUES P, HARDY J, MULLAN M: Early-onset Alzheimer's disease caused by mutations at codon 717 of the beta-amyloid precursor protein gene. *Nature* **353**: 844-846, 1991.

CHUI DH, TANAHASHI H, OZAWA K, IKEDA S, CHECLER F, UEDA O, SUZUKI H, ARAKI W, INOUE H, SHIROTANI K, TAKAHASHI K, GALLYAS F, TABIRA T: Transgenic mice with Alzheimer presenilin 1 mutations show accelerated neurodegeneration without amyloid plaque formation. *Nat Med* **5**: 560-564, 1999.

CORDER EH, SAUNDERS AM, STRITTMATTER WJ, SCHMECHEL DE, GASKELL PC, SMALL GW, ROSES AD, HAINES JL, PERICAK-VANCE MA: Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**: 921-923, 1993.

CZERNIAWSKI J, MIYASHITA T, LEWANDOWSKI G, GUZOWSKI JF: Systemic lipopolysaccharide administration impairs retrieval of context-object discrimination, but not spatial, memory: evidence for selective disruption of specific hippocampus-dependent memory functions during acute neuroinflammation. *Brain Behav Immun* **44**: 159-166, 2015.

DAULATZAI MA: Fundamental role of pan-inflammation and oxidative-nitrosative pathways in neuropathogenesis of Alzheimer's disease. *Am J Neurodegener Dis* **5**: 1-28, 2016.

DE VUGT ME, STEVENS F, AALTEN P, LOUSBERG R, JASPERS N, VERHEY FR: A prospective study of the effects of behavioral symptoms on the institutionalization of patients with dementia. *Int Psychogeriatr* **17**: 577-589, 2005.

ELMQUIST JK, SCAMMELL TE, SAPER CB: Mechanisms of CNS response to systemic immune challenge: the febrile response. *Trends Neurosci* **20**: 565-570, 1997.

ERICKSON MA, HARTVIGSON PE, MOROFUJI Y, OWEN JB, BUTTERFIELD DA, BANKS WA: Lipopolysaccharide impairs amyloid β efflux from brain: altered vascular sequestration, cerebrospinal fluid reabsorption, peripheral clearance and transporter function at the blood-brain barrier. *J Neuroinflam* **9**: 150, 2012.

ERICSSON A, KOVACS KJ, SAWCHENKO PE: A functional anatomical analysis of central pathways subserving the effects of interlukin-1 on stress-related neuroendocrine neurons. *J Neurosci* **14**: 897-913, 1994.

EXLINE MC, CROUSER ED: Mitochondrial mechanisms of sepsis induced organ failure. *Front Biosci* **13**: 5031-5041, 2008.

FAN LW, PANG Y, LIN S, TIEN LT, MA T, RHODES PG, CAI Z: Minocycline reduces lipopolysaccharide-induced neurological dysfunction and brain injury in the neonatal rat. *J Neurosci Res* **82**: 71-82, 2005.

FERRI CP, AMES D, PRINCE M, 10/66 DEMENTIA RESEARCH GROUP: Behavioral and psychological symptoms of dementia in developing countries. *Int Psychogeriatr* **16**: 441-459, 2004.

FITZPATRICK AL, KULLER LH, LOPEZ OL, KAWAS CH, JAGUST W: Survival following dementia onset: Alzheimer's disease and vascular dementia. *J Neurol Sci* **229-230**: 43-49, 2005.

FREDERIC F, OLIVER C, WOLLMAN E, DELHAYE-BOUCHARD N, MARIANI J: IL-1 and LPS induce a sexually dimorphic response of the hypothalamo pituitary-adrenal axis in several mouse strains. *Eur Cytokine Netw* **4**: 321-329, 1993.

FU HQ, YANG T, XIAO W, FAN L, WU Y, TERRANDO N, WANG TL: Prolonged neuroinflammation after lipopolysaccharide exposure in aged rats. *PLoS One* **9**: e106331, 2014.

GALLEY HF: Oxidative stress and mitochondrial dysfunction in sepsis. *Br J Anaesth* **107**: 57-64, 2011.

GANGULI M, DODGE HH, SHEN C, PANDAV RS, DEKOSKY ST: Alzheimer disease and mortality: a 15-year epidemiological study. *Arch Neurol* **62**: 779-784, 2005.

GAO HM, JIANG J, WILSON B, ZHANG W, HONG JS, LIU B: Microglial activation´s mediated delayed and progressive degeneration of rat nigral dopaminergic neurons: relevance to Parkinson's disease. *J Neurochem* **81**: 1285-1297, 2002.

GATZ M, REYNOLDS CA, FRATIGLIONI L, JOHANSSON B, MORTIMER JA, BERG S, FISKE A, PEDERSEN NL: Role of genes and environments for explaining Alzheimer disease. *Arch Gen Psychiatry* **3**: 168-174, 2006.

GHOSH S, LERTWATTANARAK R, GARDUÑO JDE J, GALEANA JJ, LI J, ZAMARRIPA F, LANCASTER JL, MOHAN S, HUSSEY S, MUSI N: Elevated muscle TLR4 expression and metabolic endotoxemia in human aging. *J Gerontol A Biol Sci Med Sc* **70**: 232-246, 2015.

GOATE A, CHARTIER-HARLIN MC, MULLAN M, BROWN J, CRAWFORD F, FIDANI L, GIUFFRA L, HAYNES A, IRVING N, JAMES L, MANT R, NEWTON P, ROOKE K, ROQUES P, TALBOT C, PERICAK-VANCE M, ROSES A, WILLIAMSON R, ROSSOR M, OWEN M, HARDY J: Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* **349**: 704-706, 1991.

GOURAS GK, TSAI J, NASLUND J, VINCENT B, EDGAR M, CHECLER F, GREENFIELD JP, HAROUTUNIAN V, BUXBAUM JD, XU H, GREENGARD P, RELKIN NR: Intraneuronal Aβ42 accumulation in human brain. *Am J Pathol* **156**: 15-20, 2000.

GRUDZIEN A, SHAW P, WEINTRAUB S, BIGIO E, MASH DC, MESULAM MM: Locus coeruleus neurofibrillary degeneration in aging, mild cognitive impairment and early Alzheimer's disease. *Neurobiol Aging* **28**: 327-335, 2007.

HABICHT GS: Body temperature in normal and endotoxin-treated mice of different ages. *Mech Ageing Dev* **16**: 97-104, 1981.

HABICHT GS: Acquired immunological tolerance in aged mice II. The cellular basis of the loss of tolerance sensitivity. *Mech Ageing Dev* **30**: 23-36, 1985.

HAILMAN E, LICHENSTEIN HS, WURFEL MM, MILLER DS, JOHNSON DA, KELLEY M, BUSSE LA, ZUKOWSKI MM, WRIGHT SD: Lipopolysaccharide (LPS)-binding protein accelerates the binding of LPS to CD14. *J Exp Med* **179**: 269-277, 1994.

HANSEN MK, NGUYEN KT, FLESHNER M, GOEHLER LE, GAYKEMA RP, MAIER SF, WATKINS LR: Effects of vagotomy on serum endotoxin, cytokines and corticosterone after intraperitoneal lipopolysaccharide. *Am J Physiol Regul Integr Comp Physiol* **278**: R331-R336, 2000.

HARDY J, SELKOE DJ: The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* **297**: 353-356, 2002.

HART BL: Biological basis of the behavior of sick animals. *Neurosci Biobehav Rev* **12**: 123-137, 1988.

HAUSS-WEGRZYNIAK B, DOBRZANSKI P, STOEHR JD, WENK GL: Chronic neuroinflammation in rats reproduces components of the neurobiology of Alzheimer's disease. *Brain Res* **780**: 294-303, 1998.

HAUSS-WEGRZYNIAK B, VANNUCCHI MG, WENK GL: Behavioral and ultrastructural changes induced by chronic neuroinflammation in young rats. *Brain Res* **859**: 157-166, 2000.

HENNIGAN A, TROTTER C, KELLY AM: Lipopolysaccharide impairs long-term potentiation and recognition memory and increases p75NTR expression in the rat dentate gyrus. *Brain Res* **1130**: 158-166, 2007.

HIROSE Y, IMAI Y, NAKAJIMA K, TAKEMOTO N, TOYA S, KOHSAKA S: Glial conditioned medium alters the expression of amyloid precursor protein in SH-SY5Y neuroblastoma cells. *Biochem Biophys Res Commun* **198**: 504-509, 1994.

HOOZEMANS JJ, ROZEMULLER AJ, JANSSEN I, DE GROOT CJ, VEERHUIS R, EIKELENBOOM P: Cyclooxygenase expression in microglia and neurons in Alzheimer's disease and control brain. *Acta Neuropathol (Berl)* **101**: 2-8, 2001.

HOUDEK HM, LARSON J, WATT JA, ROSENBERGER TA: Bacterial lipopolysaccharide induces a dose-dependent activation of neuroglia and loss of basal forebrain cholinergic cells in the rat brain. *Inflamm Cell Signal* **1**: e47, 2014.

IQBAL K, GRUNDKE-IQBAL I: Discoveries of tau, abnormally hyperphosphorylated tau and others of neurofibrillary degeneration: a personal historical perspective. *JAD* **9**: 219-242, 2006.

IRVINE GB, EL-AGNAF OM, SHANKAR GM, WALSH DM: Protein aggregation in the brain: the molecular basis for Alzheimer's and Parkinson's diseases. *Mol Med* **14**: 451-464, 2008.

JAEGER LB, DOHGU S, SULTANA R, LYNCH JL, OWEN JB, ERICKSON MA, SHAH GN, PRICE TO, FLEEGAL-DEMOTTA MA, BUTTERFIELD DA, BANKS WA: Lipopolysaccharide alters the blood-brain barrier transport of amyloid beta protein: a mechanism for inflammation in the progression of Alzheimer's disease. *Brain Behav Immun* **23**: 507-517, 2009.

JANG JH, SURH YJ: Beta-amyloid-induced apoptosis is associated with cyclooxygenase-2 up-regulation via the mitogen-activated protein kinase-NF-kappaB signaling pathway. *Free Radic Biol Med* **38**: 1604-1613, 2005.

JOSHI R, GARABADU D, TEJA GR, KRISHNAMURTHY S: Silibinin ameliorates LPS-induced memory deficits in experimental animals. *Neurobiol Learn Mem* **116**: 117-131, 2014.

KENT S, BLUTHE R-M, KELLEY KW, DANTZER R: Sickness behaviour as a new target for drug development. *Trends Pharmacol Sci* **13**: 24-28, 1992.

KLEIN SL, NELSON RJ: Activation of the immune-endocrine system with lipopolysaccharide reduces affiliative behaviours involves. *Behav Neurosci* **113**: 1042-1048, 1999.

KOBAYASHI K, HERNANDEZ LD, GALAN JE, JANEWAY CA JR, MEDZHITOV R, FLAVELL RA: IRAK-M is a negative regulator of Toll-like receptor signaling. *Cell* **110**: 191-202, 2002.

LECANU L, PAPADOPOULOS V: Modelling Alzheimer's disease with non-transgenic rat models. *Alzheimers Res Ther* **5**: 17, 2013.

LEE JW, LEE YK, YUK DY, CHOI DY, BAN SB, OH KW, HONG JT: Neuro-inflammation induced by lipopolysaccharide causes cognitive impairment through enhancement of beta-amyloid generation. *J Neuroinflam* **5**: 37, 2008.

LEHNARDT S, MASSILLON L, FOLLETT P, JENSEN FE, RATAN R, ROSENBERG PA, VOLPE JJ, VARTANIAN T: Activation of innate immunity in the CNS triggers neurodegeneration through a toll-like receptor 4-dependent pathway. *Proc Natl Acad Sci U S A* **100**: 8514-8519, 2003.

LEVY-LAHAD E, WASCO W, POORKAJ P, ROMANO DM, OSHIMA J, PETTINGELL WH, YU C, JONDRO PD, SCHMIDT SD, WANG K, CROWLEY AC, FU Y-H, GUENETTE SY, GALAS D, NEMENS E, WIJSMAN EM, BIRD TD, SCHELLENBERG GD, TANZI RE: Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science* **269**: 973-977, 1995.

LOWES DA, WEBSTER NR, MURPHY MP, GALLEY HF: Antioxidants that protect mitochondria reduce interleukin-6 and oxidative stress, improve mitochondrial function, and reduce biochemical markers of organ dysfunction in a rat model of acute sepsis. *B J Anaesth* **110**: 472-480, 2013.

MAITRA U, DENG H, GLAROS T, BAKER B, CAPELLUTO DG, LI Z, LI L: Molecular mechanisms responsible for the selective and low-grade induction of proinflammatory mediators in murine macrophages by lipopolysaccharide. *J Immunol* **189**: 1014-1023, 2012.

MEYER U: Prenatal poly (I:C) exposure and other developmental immune activation models in rodent systems. *Biol Psychiatry* **75**: 307-315, 2014.

MIKLOSSY J: Chronic inflammation and amyloidogenesis in Alzheimer's disease - role of spirochetes. *JAD* **13**: 381-391, 2008.

MIZUNO T, SAWADA M, MARUNOUCHI T, SUZUMURA A: Production of interleukin-10 by mouse glial cells in culture. *Biochem Biophys Res Commun* **205**: 1907-1915, 1994.

MULLAN M, CRAWFORD F, AXELMAN K, HOULDEN H, LILIUS L, WINBLAD B, LANNFELT L: A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of beta-amyloid. *Nat Genet* **1**: 345-347, 1992.

NGUYEN KT, DEAK T, OWENS SM, KOHNO T, FLESHNER M, WATKINS LR, MAIER SF: Exposure to acute stress induces brain interleukin-1 beta protein in the rat. *J Neurosci* **18**: 2239-2246, 1998.

OBERMEYER TS, YONICK D, LAUING K, STOCK SR, NAUER R, STROTMAN P, SHANKAR R, GAMELLI R, STOVER M, CALLACI JJ: Mesenchymal stem cells facilitate fracture repair in an alcohol-induced impaired healing model. *J Orthop Trauma* **26**: 712-718, 2012.

OHANIAN SH, SCHWAB JH: Persistence of group a streptococcal cell walls related to chronic inflammation of rabbit dermal connective tissue. *J Exp Med* **125**: 1137-1148, 1967.

OITZL MS, VAN OERS H, SCHOBITZ B, DE KLOET WR: Interlukin-1 beta, but not interlukin-6, impairs spatial navigation learning. *Brain Res* **613**: 160-163, 1993.

PANG Y, FAN LW, ZHENG B, CAI Z, RHODES PG: Role of interleukin-6 in lipopolysaccharide-induced brain injury and behavioral dysfunction in neonatal rats. *Neuroscience* **141**: 745-755, 2006.

PARIS D, TOWNSEND KP, OBREGON DF, HUMPHREY J, MULLAN M: Pro-inflammatory effect of freshly solubilized beta-amyloid peptides in the brain. *Prostaglandins Other Lipid Mediat* **70**: 1-12, 2002.

PASINETTI GM: Cyclooxygenase and Alzheimer's disease: implications for preventive initiatives to slow the progression of clinical dementia. *Arch Gerontol Geriatr* **33**: 13-28, 2001.

PASINETTI GM: From epidemiology to therapeutic trials with antiinflammatory drugs in Alzheimer's disease: the role of NSAIDs and cyclooxygenase in beta-amyloidosis and clinical dementia. *JAD* **4**: 435-445, 2002.

PASINETTI GM, AISEN PS: Cyclooxygenase-2 expression is increased in frontal cortex of Alzheimer's disease brain. *Neuroscience* **87**: 319-324, 1998.

PETRASEK T, SKURLOVA M, MALENINSKA K, VOJTECHOVA I, KRISTOFIKOVA Z, MATUSKOVA H, SIROVA J, VALES K, RIPOVA D, STUCHLIK A: A rat model of Alzheimer´s disease based on abeta42 and pro-oxidative substances exhibits cognitive deficit and alterations in glutamatergic and cholinergic neurotransmitter systems. *Front Aging Neurosci* **8**: 83, 2016.

POWELL SB: Models of neurodevelopmental abnormalities in schizophrenia. *Curr Top Behav Neurosci* **4**: 435-481, 2010.

PUGH CR, KUMAGAWA K, FLESHNER M, WATKINS LR, MAIER SF, RUDY JW: Selective effects of peripheral lipopolysaccharide administration on contextual and auditory-cue fear conditioning. *Brain Behav Immun* **12**: 212-229, 1998.

RIVEST S: Regulation of innate immune responses in the brain. *Nat Rev Immunol* **9**: 429-439, 2009.

ROSSOR MN, FOX NC, FREEBOROUGH PA: Clinical features of sporadic and familial Alzheimer's disease. *Neurodegeneration* **5**: 393-397, 1996.

SADIGH-ETEGHAD S, TALEBI M, FARHOUDI M: Association of apolipoprotein E epsilon 4 allele with sporadic late onset Alzheimer's disease. A meta-analysis. *Neurosciences (Riyadh)* **17**: 321-326, 2012.

SASTRE M, DEWACHTER I, LANDRETH GE, WILLSON TM, KLOCKGETHER T, VAN LEUVEN F, HENEKA MT: Nonsteroidal anti-inflammatory drugs and peroxisome proliferator-activated receptor-gamma agonists modulate immunostimulated processing of amyloid precursor protein through regulation of beta-secretase. *J Neurosci* **23**: 9796-9804, 2003.

SAUTER C, WOLFENSBERGER C: Interferon in human serum after injection of endotoxin. *Lancet* **2**: 852-853, 1980.

SCHELLENBERG GD, BIRD TD, WIJSMAN EM, ORR HT, ANDERSON L, NEMENS E, WHITE JA, BONNYCASTLE L, WEBER JL, ALONSO ME, POTTER H, HESTON LL, MARTIN GM: Genetic linkage evidence for a familial Alzheimer's disease locus on chromosome 14. *Science* **258**: 668-671, 1992.

SCHMID CD, MELCHIOR B, MASEK K, PUNTAMBEKAR SS, DANIELSON PE, LO DD, SUTCLIFFE JG, CARSON MJ: Differential gene expression in LPS/IFNgamma activated microglia and macrophages: in vitro versus in vivo. *J Neurochem* **109**: 117-125, 2009.

SHAW KN, COMMINS ST, O'MARA SM: Lipopolysaccharide causes deficits in spatial learning in the water maze but not in BDNF expression in the rat dentate gyrus. *Behav Brain Res* **124**: 47-54, 2001.

SHAW KN, COMMINS ST, O'MARA SM: Cyclooxygenase inhibition attenuates endotoxin-induced spatial learning deficits, but not an endotoxin-induced blockade of long-term potentiation. *Brain Res* **1038**: 231-237, 2005.

SHENG JG, BORA SH, XU G, BORCHELT DR, PRICE DL, KOLIATSOS VE: Lipopolysaccharide induced-neuroinflammation increases intracellular accumulation of amyloid precursor protein and amyloid beta peptide in APPswe transgenic mice. *Neurobiol Dis* **14**: 133-145, 2003.

SHERRINGTON R, ROGAEV EI, LIANG Y, ROGAEVA EA, LEVESQUE G, IKEDA M, CHI H, LIN C, LI G, HOLMAN K, TSUDA T, MAR L, FONCIN JF, BRUNI AC, MONTESI MP, SORBI S, RAINERO I, PINESSI L, NEE L, CHUMAKOV I, POLLEN D, BROOKES A, SANSEAU P, POLINSKY RJ, WASCO W, DA SILVA HA, HAINES JL, PERKICAK-VANCE MA, TANZI RE, ROSES AD, FRASER PE, ROMMENS JM, ST GEORGE-HYSLOP PH: Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease *Nature* **375**: 754-760, 1995.

SONG X, ZHOU B, ZHANG P, LEI D, WANG Y, YAO G, HAYASHI T, XIA M, TASHIRO S, ONODERA S, IKEJIMA T: Protective effect of silibinin on learning and memory impairment in LPS-treated rats via ROS-BDNF-TrkB pathway. *Neurochem Res* **41**: 1662-1672, 2016.

SPARKMAN NL, MARTIN LA, CALVERT WS, BOEHM GW: Effects of intraperitoneal lipopolysaccharide on Morris maze performance in year-old and 2-month-old female C57BL/6J mice. *Behav Brain Res* **159**: 145-151, 2005.

SPINEDI E, CHISARI A, PRALONG F, GAILLARD RC: Sexual dimorphism in the mouse hypothalamic-pituitary-adrenal axis function after endotoxin and insulin stresses during development. *Neuroimmunomodulation* **4**: 77-83, 1997.

STRITTMATTER WJ, SAUNDERS AM, SCHMECHEL D, PERICAK-VANCE M, ENGHILD J, SALVESEN GS, ROSES AD: Apolipoprotein E: High-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A* **90**: 1977-1981, 1993.

SUN J, ZHANG S, ZHANG X, ZHANG X, DONG H, QIAN Y: IL-17A is implicated in lipopolysaccharide-induced neuroinflammation and cognitive impairment in aged rats via microglial activation. *J Neuroinflam* **12**: 165, 2015.

SZABADOS T, DUL C, MAJTÉNYI K, HARGITAI J, PÉNZES Z, URBANICS R: A chronic Alzheimer´s model evoked by mitochondrial poison sodium azide for pharmacological investigations. *Behav Brain Res* **154**: 31-40, 2004.

TAKEMURA T, MAKINO S, TAKAO T, ASABA K, SUEMARU S, HASHIMOTO K: Hypothalamic-pituitary-adrenocortical responses to single vs. repeated endotoxin lipopolysaccharide administration in the rat. *Brain Res* **767**: 181-191, 1997.

TANSEY MG, McCOY MK, FRANK-CANNON TC: Neuroinflammatory mechanisms in Parkinson's disease: Potential environmental triggers, pathways, and targets for early therapeutic intervention. *Exp Neurol* **208**: 1-25, 2007.

TAVEIRA DA SILVA AM, KAULBACH HC, CHUIDIAN FS, LAMBERT DR, SUFFREDINI AF, DANNER RL: Brief report: shock and multiple-organ dysfunction after self-administration of Salmonella endotoxin. *N Engl J Med* **328**: 1457-1460, 1993.

VASCONCELOS AR, YSHII LM, VIEL TA, BUCK HS, MATTSON MP, SCAVONE C, KAWAMOTO EM: Intermittent fasting attenuates lipopolysaccharide-induced neuroinflammation and memory impairment. *J Neuroinflam* **11**: 85, 2014.

VASSAR R: The beta-secretase, BACE: a prime drug target for Alzheimer's disease. *J Mol Neurosci* **17**: 157-170, 2001.

VÍCTOR VM, ESPULGUES JV, HERNÁNDEZ-MIJARES A, ROCHA M: Oxidative stress and mitochondrial dysfunction in sepsis: a potential therapy with mitochondria-targeted antioxidants. *Infect Disord Drug Targets* **9**: 376-389, 2009.

WALTER J, KAETHER C, STEINER H, HAASS C: The cell biology of Alzheimer's disease: uncovering the secrets of secretases. *Curr Opin Neurobiol* **11**: 585-590, 2001.

WALTER S, DOERING A, LETIEMBRE M, LIU Y, HAO W, DIEM R, BERNREUTHER C, GLATZEL M, ENGELHARDT B, FASSBENDER K: The LPS receptor, CD14 in experimental autoimmune encephalomyelitis and multiple sclerosis. *Cell Physiol Biochem* **17**: 167-172, 2006.

WARREN HS, FITTING C, HOFF E, ADIB-CONQUY M, BEASLEY-TOPLIFFE L, TESINI B, LIANG X, VALENTINE C, HELLMAN J, HAYDEN D, CAVAILLON JM: Resilience to bacterial infection: difference between species could be due to proteins in serum. *J Infect Dis* **201**: 223-232, 2010.

WATERHOUSE U, ROPER VE, BRENNAN KA, ELLENBROEK BA: Nicotine ameliorates schizophrenia-like cognitive deficits induced by maternal LPS exposure: a study in rats. *Dis Model Mech* **9**: 1159-1167, 2016.

WELSER-ALVES JV, MILNER R: Microglia are the major source of TNF-α and TGF-β1 in postnatal glial cultures; regulation by cytokines, lipopolysaccharide, and vitronectin. *Neurochem Int* **63**: 47-53, 2013.

WHITTON PS: Inflammation as a causative factor in the aetiology of Parkinson's disease. *Brit J Pharmacol* **150**: 963-976, 2007.

WILKINS RH, BRODY IA: Alzheimer's disease. *Arch Neurol* **21**: 109-110, 1969.

WIRTHS O, MULTHAUP G, CZECH C, BLANCHARD V, MOUSSAOUI S, TREMP G, PRADIER L, BEYREUTHER K, BAYER TA: Intraneuronal Abeta accumulation precedes plaque formation in beta-amyloid precursor protein and presenilin-1 double-transgenic mice. *Neurosci Lett* **306**: 116-120, 2001.

YAMADA K, KOMORI Y, TANAKA T, SENZAKI K, NIKAI T, SUGIHARA H, KAMEYAMA T, NABESHIMA T: Brain dysfunction associated with an induction of nitric oxide synthase following an intracerebral injection of lipopolysaccharide in rats. *Neuroscience* **88**: 281-294, 1999.

YASUDA N, GREER MA: Evidence that the hypothalamus mediates endotoxin stimulation of adrenocorticotrophic hormone secretion. *Endocrinology* **102**: 947-953, 1978.

ZHANG Y-H, LU J, ELMQUIST JK, SAPER CB: Lipopolysaccharide activates specific populations of hypothalamic and brainstem neurons that project to the spinal cord. *J Neurosci* **20**: 6578-6586, 2000.

ZHAO W, XIE W, LE W, BEERS DR, HE Y, HENKEL JS, SIMPSON EP, YEN AA, XIAO Q, APPEL SH: Activated microglia initiate motor neuron injury by a nitric oxide and glutamate-mediated mechanism. *J Neuropathol Exp Neurol* **63**: 964-977, 2004.

ZHU B, WANG ZG, DING J, LIU N, WANG DM, DING LC, YANG C: Chronic lipopolysaccharide exposure induces cognitive dysfunction without affecting BDNF expression in the rat hippocampus. *Exp Ther Med* **7**: 750-754, 2014.