Inflammopharmacol (2016) 24:291–293
DOI 10.1007/s10787-016-0283-2

Inflammopharmacology

COMMENTARY

LPS and neuroinflammation: a matter of timing

Patricia C. Lopes[1]

Received: 6 September 2016 / Accepted: 8 September 2016 / Published online: 19 September 2016

Abstract Lipopolysaccharide (LPS) administration has been repeatedly shown to elicit central inflammation, regardless of the route of administration. In a recent study, Tiwari et al. (Inflammopharmacology 10.1007/s10787-016-0274-3, 2016) dispute the potential of peripheral administration of LPS to induce neuroinflammation. Here, I summarise literature indicating that the neuroinflammatory effects of LPS are time dependent, and suggest that their findings can be explained by the time at which they chose to measure neuroinflammation.

Keywords Neuroinflammation · Lipopolysaccharide · Time-dependent effects

Lipopolysaccharide (LPS) is a component of Gram-negative bacterial cell wall. Once recognized by the immune system, LPS elicits a proinflammatory response (Zhang and Ghosh 2000) and has thus become extensively used in research for this purpose (e.g., van Dam et al. 1992; Gatti and Bartfai 1993; Laye et al. 1994; Breder et al. 1994; Quan et al. 1999). In particular, inflammation within the brain (neuroinflammation) can be obtained by central or peripheral administration of LPS (Rivest 2003). However, Tiwari et al. (2016) recently reported not observing neuroinflammatory effects of peripheral LPS administration (via repeated intraperitoneal injections) to rats. Why this discrepancy with the previous literature?

✉ Patricia C. Lopes
patricia.lopes@ieu.uzh.ch

[1] Department of Evolutionary Biology and Environmental Studies, University of Zurich, Zurich, Switzerland

While it is common knowledge that negative results are less frequently published (Fanelli 2012), a close look at the literature (Table 1) demonstrates that the results of this study have an alternative explanation. In Table 1, I have summarized only the studies cited within Tiwari et al. (2016), where peripheral injection of LPS was used. Based on this table, it is possible to make two important observations: (1) within the range of doses of LPS administered in those studies (from 100 to 10,000 μg/kg), Tiwari et al. (2016) used one of the lowest doses (125 μg/kg, i.e., about 100 times less then the high end of the spectrum) and (2) studies using low doses of LPS have found neuroinflammatory effects within a short period of time post-injection (few hours), while studies using high doses have found neuroinflammatory effects in both the short- (few hours) and long-term (months). Tiwari et al. (2016) collected brain samples at a relatively long time period post-injection.

Most studies in Table 1 do not reveal whether low doses of LPS elicit long-term responses, but there are two studies that do so. In the study by Biesmans et al. (2013), where several LPS doses were tested, the authors quantified neuroinflammatory effects of one intraperitoneal injection of LPS over time. The findings reveal that, at the dose of 630 μg/kg, a dose five times higher than that of Tiwari et al. (2016), several effects within the brain have already subsided at 24 h post-LPS injection. Similar results were obtained by Spulber et al. (2012), at a lower dose (330 μg/kg). Tiwari et al. (2016) collected their brain samples at 48 h after their last administration of LPS. Given the low dose and the time of collection, they should no longer observe neuroinflammatory changes, which they did not. Notably, a study in rats (Quan et al. 1999) found inflammation in certain brain regions 2 h post intravenous administration, using a dose of LPS more than ten times

Table 1 Articles cited by Tiwari et al. (2016), where peripheral LPS administration was employed and respective examples of the alteration in the neuroinflammatory markers quantified

LPS doses (μg/kg)	Study animal	Brain sample collection: time post-injection	Neuroinflammatory markers changed	References
100	Rat	4 h	GSH	Abdel-Salam et al. 2012
125	**Rat**	**2 days**	**None**	**Tiwari et al. 2016**
330	Mouse	4 h	IL-1β, IL6	Godbout et al. 2005
330	Mouse	4 h	IL-1β, IL-6, IDO	Henry et al. 2008
330	Mouse	2, 4, 24 and 48 h	Several, including IL-1β, TNFα, IL-6, IL-10 elevated at 2 or 4 h relative to control, but back to baseline by 24 or 48 h; iNOS up at 2 h and down at 48 h	Spulber et al. 2012
Several-focus here on 630	Mouse	2, 6, 24 h	Several, including IL-6 and TNFα elevated at 2 and 6 h, back to baseline at 24 h; MCP-1 elevated at all time points	Biesmans et al. 2013
1.000	Mouse	2 h	IL-1β	Pollak et al. 2005
1.000	Mouse	2 h	IL-2	Tyagi et al. 2007
2.000	Rat (aged)	1, 3, 7 and 30 days	NF-κBp65, TNFα, IL-1β (the timeline for gene and protein levels differs)	Fu et al. 2014
2.000	Mouse	24 h	IL-1β, IL-6, TNFα, CCL2	Cazareth et al. 2014
5.000	Rat	7 days; 10 months	TNFα, IL-18	Bossù et al. 2012
5.000	Mouse[a]	0.5, 1, 2, 3, 6 and 9 h; 10 months	Several, including TNFα elevated at all time points	Qin et al. 2007
10.000	Rat	1, 3, 7, and 16 days	NF-κBp65, all time points	Fan et al. 2014
10.000	Rat	4, 8 and 24 h	Number of iNOS-immunoreactive cells elevated at 24 h	Semmler et al. 2005

For ease of comparison the study by Tiwari et al. (2016) is highlighted in bold

Studies where collection time point was not evident or clearly stated are not reported in the table (this includes references to review articles)

LPS doses have been converted to μg/kg for purposes of comparison

CCL2 chemokine (C–C motif) ligand 2, *GSH* glutathione, *IDO* indoleamine 2, 3 dioxygenase, *IL* interleukin, *iNOS* inducible nitric oxide synthase, *MCP-1* monocyte chemoattractant protein-1, *NF* nuclear factor, *TNF* tumor necrosis factor

[a] Only considering results for the wild-type mice

lower than the one used by Tiwari et al. (2016). Therefore, while the authors write that their finding of a lack of neuroinflammatory effect cannot be attributed to dosage or short- versus long-term effects of LPS, it is likely that it can in fact be attributed to the combination of these two variables. Thus, their conclusion that "LPS (i.p.) administration is devoid of any neuroinflammatory effects" should be placed in the context of the dose used and the timing they chose to collect their samples. Finally, the title of their article "Redefining the role of peripheral LPS as a neuroinflammatory agent…" must be considered carefully—the role of LPS cannot be redefined based solely on a single study where a low dosage has been administered and where samples are collected after a long time period has elapsed. Combined, the study by Tiwari et al. (2016) and the literature summarized here should serve as a warning for future studies about the importance of considering both dose and timing when neuroinflammatory effects are expected.

References

Abdel-Salam OM, Abdel-Rahman RF, Sleem AA, Farrag AR (2012) Modulation of lipopolysaccharide-induced oxidative stress by capsaicin. Inflammopharmacology 20:207–217

Biesmans S, Meert TF, Bouwknecht JA, Acton PD, Davoodi N, de Haes P, Kuijlaars J, Langlois X, Matthews LJ, Ver Donck L

(2013) Systemic immune activation leads to neuroinflammation and sickness behavior in mice. Mediat Inflamm 2013:271359

Bossù P, Cutuli D, Palladino I, Caporali P, Angelucci F, Laricchiuta D, Gelfo F, de Bartolo P, Caltagirone C, Petrosini L (2012) 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 Neuroinflamm 9:101

Breder CD et al (1994) Regional induction of tumor necrosis factor alpha expression in the mouse brain after systemic lipopolysaccharide administration. Proc Natl Acad Sci USA 91:11393–11397

Cazareth J, Guyon A, Heurteaux C, Chabry J, Petit-Paitel A (2014) Molecular and cellular neuroinflammatory status of mouse brain after systemic lipopolysaccharide challenge: importance of CCR2/CCL2 signaling. J Neuroinflamm 11:132

Fan L, Wang T, Chang L, Song Y, Wu Y, Ma D (2014) Systemic inflammation induces a profound long term brain cell injury in rats. Acta Neurobiol Exp 74:298–306

Fanelli D (2012) Scientometrics 90:891. doi:10.1007/s11192-011-0494-7

Fu HQ, Yang T, Xiao W, Fan L, Wu Y, Terrando N, Wang TL (2014) Prolonged neuroinflammation after lipopolysaccharide exposure in aged rats. PLoS One 9:e106331

Gatti S, Bartfai T (1993) Induction of tumor necrosis factor-alpha mRNA in the brain after peripheral endotoxin treatment: comparison with interleukin-1 family and interleukin-6. Brain Res 624:291–294

Godbout J, Chen J, Abraham J, Richwine A, Berg B, Kelley K, Johnson R (2005) Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. FASEB J 19:1329–1331

Henry CJ, Huang Y, Wynne A, Hanke M, Himler J, Bailey MT, Sheridan JF, Godbout JP (2008) Minocycline attenuates lipopolysaccharide (LPS)-induced neuroinflammation, sickness behavior, and anhedonia. J Neuroinflammation 5:2094–2095

Laye S, Parnet P, Goujon E, Dantzer R (1994) Peripheral administration of lipopolysaccharide induces the expression of cytokine transcripts in the brain and pituitary of mice. Brain Res Mol Brain Res 27:157–162

Pollak Y, Gilboa A, Ben-Menachem O, Ben-Hur T, Soreq H, Yirmiya R (2005) Acetylcholinesterase inhibitors reduce brain and blood interleukin-1β production. Ann Neurol 57:741–745

Qin L, Wu X, Block ML, Liu Y, Breese GR, Hong JS, Knapp DJ, Crews FT (2007) Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia 55:453–462

Quan N, Stern EL, Whiteside MB, Herkenham M (1999) Induction of pro-inflammatory cytokine mRNAs in the brain after peripheral injection of subseptic doses of lipopolysaccharide in the rat. J Neuroimmunol 93:72–80

Rivest S (2003) Molecular insights on the cerebral innate immune system. Brain Behav Immun 17:13–19. doi:10.1016/s0889-1591(02)00055-7

Semmler A, Okulla T, Sastre M, Dumitrescu-Ozimek L, Heneka MT (2005) Systemic inflammation induces apoptosis with variable vulnerability of different brain regions. J Chem Neuroanat 30:144–157

Spulber S, Edoff K, Hong L, Morisawa S, Shirahata S, Ceccatelli S (2012) Molecular hydrogen reduces LPS-induced neuroinflammation and promotes recovery from sickness behaviour in mice. PLoS One 7:e42078

Tiwari V, Singh M, Rawat JK et al (2016) Inflammopharmacology. doi:10.1007/s10787-016-0274-3

Tyagi E, Agrawal R, Nath C, Shukla R (2007) Effect of anti-dementia drugs on LPS induced neuroinflammation in mice. Life Sci 80:1977–1983

van Dam AM, Brouns M, Louisse S, Berkenbosch F (1992) Appearance of interleukin-1 in macrophages and in ramified microglia in the brain of endotoxin-treated rats: a pathway for the induction of non-specific symptoms of sickness? Brain Res 588:291–296

Zhang G, Ghosh S (2000) Molecular mechanisms of NF-kappaB activation induced by bacterial lipopolysaccharide through Toll-like receptors. J Endotoxin Res 6:453–457. doi:10.1179/096805100101532414