Neuroinflammatory changes negatively impact on LTP: a focus on IL-1β

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Abstract

In recent years it has become clear that neuroinflammatory changes develop in the brain with age and that similar, though more profound changes, occur in neurodegenerative conditions and in animal models of neurodegeneration. These changes are linked with deterioration in plasticity and the evidence suggests that a key causative factor is microglial activation and the associated increase in production and release of inflammatory cytokines. Several groups have reported that interleukin (IL)-1β negatively impacts on hippocampal-dependent learning and has an inhibitory effect on LTP although this is concentration-dependent. Similarly other inflammatory cytokines, which are also produced by microglia similarly decrease LTP. The evidence supporting these findings will be reviewed here and will be discussed in the context of considering mechanisms by which the negative impact of neuroinflammation can be ameliorated.

IL-1β negatively impacts on synaptic plasticity - the historical perspective

It was recognized in the late 1980s and early 1990s that the inflammatory cytokine, interleukin (IL)-1, was an endogenous pyrogen and that it interacted with centrally-located IL-1 receptors to induce the behavioural changes that accompanied fever (Blatteis, 1988; Kluger, 1991). At around the same time, the first reports indicating that IL-1β exerted a negative effect on LTP in vitro appeared. Thus application of IL-1β to hippocampal slices inhibited LTP in CA1 (Bellinger et al., 1993) and CA3 (Katsuki et al., 1990). A similar negative effect of IL-1β on LTP in dentate gyrus was reported subsequently (Cunningham et al., 1996) and, in this case, it was proposed that the IL-1β-induced change was mediated by the inhibitory effect of the cytokine on calcium channel activity. The negative effect of IL-1β on LTP was also described in vivo; intracerebroventricular injection of IL-1β inhibited LTP in perforant path-granule cell synapses in urethane-anaesthetized rats (Kelly et al., 2001; Lynch, 1998; Murray and Lynch, 1998a; Vereker et al., 2000b), while the endogenous receptor antagonist, IL-1ra, attenuated the IL-1β-induced changes (Loscher et al., 2003).

In addition to its inhibitory effects on LTP, IL-1β has also been shown to inhibit hippocampal-dependent learning, for example spatial learning (Oitzl et al., 1993 Gahtan and Overmier, 2001; Gibertini, 1998), and contextual fear conditioning (Maier and Watkins, 1995; Pugh et al., 1998; 1999; 2000). IL-1ra has been shown to attenuate the impairment in contextual fear conditioning induced by immunodeficiency virus-1 coat protein gp120, which may be mediated by IL-1β (Pugh et al., 2000). In contrast, hippocampal-independent forms of learning like auditory-cue fear conditioning, are insensitive to IL-1β (Pugh et al., 2000). Consistent with these data that describe a negative impact of IL-1β on cognition, a mouse model in which IL-1β is overexpressed displayed impairment in contextual fear conditioning but hippocampal-independent tasks were not affected (Hein et al., 2010; Hein et al., 2012)

The signaling events induced by IL-1β have been studied in detail (Dunne and O'Neill, 2003) with clear evidence that it activates members of the MAP kinase family. It has been shown that intracerebroventricular injection of IL-1β increases activation of p38 MAP kinase and JNK in hippocampus and inhibition of p38 MAP kinase by SB203580, or JNK by SP600125, attenuated the IL-1β-induced inhibition of LTP in vivo and in vitro (Curran et al., 2003; Kelly et al., 2003). IL-1β also activates NFκB and the finding that the IL-1β-induced inhibition of LTP was suppressed by the non-specific NFκB inhibitor, SN50, suggests that a number of IL-1β-induced signaling events combine to impact on LTP (Kelly et al., 2003). Interestingly, IL-1β also impacts on BDNF-induced signaling in a

p38-dependent manner (Tong et al., 2012). The authors of this work suggested that the key effect of IL-1β was to prevent the BDNF-dependent phosphorylation of insulin receptor substrate 1 which mediates the signal transduction effects of TrkB that rely on activation of CREB, Arc and cofilin.

The effect of IL-1β on LTP is dose-dependent

Some time after the initial findings that indicated a negative effect of IL-1β on LTP, a number of papers provided data demonstrating that the IL-1β-induced change is probably dose-dependent since blocking IL-1R by IL-1ra also decreased LTP (Goshen et al., 2007; Loscher et al., 2003; Schneider et al., 1998; Spulber et al., 2009) and a temperature-dependent effect of IL-1ra on LTP was also described (Ross et al., 2003). It was therefore suggested that physiological levels of IL-1 are necessary for induction and maintenance of LTP and this was confirmed by Avital and colleagues who showed that LTP was absent in perforant path granule cell synapses in anaesthetized IL-1R knockout mice and also in area CA1 in slices prepared from these mice (Avital et al., 2003). However transplantation of neural precursor cells that differentiated into astrocytes, obtained from wild type neonatal mice, were also effective in correcting the deficit in LTP observed in IL-1RI knockout mice (Ben Menachem-Zidon et al., 2011). Whether these studies imply that the loss of IL-1RI is associated with loss of cells or decreased cell viability remains to be determined. The studies of the Yirmiya group identified a close correlation between the ability of mice to sustain LTP and their performance in spatial learning tasks. Interestingly environmental enrichment, which has a beneficial effect on LTP, principally because of its ability to increase BDNF and stimulate neurogenesis (Bekinschtein et al., 2011; Eckert and Abraham, 2010), was capable of supporting LTP and spatial memory in IL-1R1 knock out mice (Goshen et al., 2009). Neither BDNF expression nor neurogenesis were affected in IL-1R1 knock out mice but the authors suggested that environmental enrichment induced its effect because it increased dendritic spine size (Goshen et al., 2009). Therefore the implication is that certain morphological changes can compensate for the loss of IL-1 receptors although the mechanism by which this occurs requires examination.

When IL-1β is increased LTP is decreased

A correlation between IL-1β concentration in hippocampus and impaired LTP has been identified in a number of models. For example, it has been widely reported that lipopolysaccharide (LPS) increases production of inflammatory cytokines in brain areas including hippocampus and many groups have reported LTP (Kelly et al., 2003; Lante et al., 2008; Maggio et al., 2013; Vereker et al., 2000a) and spatial learning (Lante et al., 2008; Shaw et al., 2001) deficits in LPS-treated animals. Strategies that attenuated the LPS-induced change in IL-1β and deficits in LTP and/or spatial learning include glucagon-like peptide-1 (Iwai et al., 2014), activation of mineralocorticoid receptors (Maggio et al., 2013), overexpression of mitochondrial transcription factor A (Hayashi et al., 2008), and treatment with N-acetylcysteine (Lante et al., 2008), CD200Fc (Cox et al., 2012), atorvastatin (Clarke et al., 2008), inhibitors of JNK (Barry et al., 2005), and p38 (Kelly et al., 2003) and the anti-inflammatory cytokine, IL-10 (Kelly et al., 2001).

The deficit in LTP in transgenic mouse models of Alzheimer's disease (AD) has also been associated with increased expression of IL-1β (Gallagher et al., 2012; Gallagher et al., 2013; Kelly et al., 2013) while administration of Aβ, which inhibits LTP, increase hippocampal concentration of IL-1β (Clarke et al., 2007; Lyons et al., 2007). Recent evidence has indicated that administration of an IL-1R blocking antibody improved synaptic plasticity in an animal model of AD (Kitazawa et al., 2011) .

There are other examples in the literature which link poor ability of animals to sustain LTP with increased hippocampal concentration of IL-1β, for example aged animals (Griffin et al., 2006; Liu et al., 2012; Murray and Lynch, 1998a) and animals exposed to stress or to γ-irradiation (Lonergan et al., 2002; Vereker et al., 2001). In each of these situations, the deficit in LTP was ameliorated when hippocampal concentration of IL-1β was decreased, for example by treating animals with the polyunsaturated fatty acid, eicosapentaenoic acid, or by decreasing reactive oxygen species production (Lonergan et al., 2002; Lynch et al., 2007; Lynch, 2010; Vereker et al., 2001).

It has been reported that aged animals are more susceptible to immune challenge and this is closely correlated with increased IL-1β concentration in the brain. For example abdominal surgery negatively impacted on hippocampal-dependent tasks in aged, but not young, rats and this effect was blocked by central administration IL-1ra (Barrientos et al., 2012), while E. coli infection similarly affected hippocampal-dependent memory in 24 month-old but not 3 month-old rats (Barrientos et al., 2006). LPS, which increases IL-1β concentration in hippocampus, stimulated cytokine production to a greater extent in hippocampus of aged mice compared with young mice and this was coupled with more profound sickness behaviour (Godbout et al., 2005) and impaired performance in a spatial learning task (Chen et al., 2008).

IL-1β, IL-18, the inflammasome and LTP

Apart from IL-1β, IL-18 has been shown to inhibit LTP. Indeed the IL-18-induced attenuation of LTP in dentate gyrus in vitro and its ability to decrease NMDA receptor-mediated potentials were both blocked by IL-1ra, although the inhibitory effect of TNFα on LTP was unaffected (Curran and O'Connor, 2001). It was subsequently reported that the inhibitory effect of IL-18 on LTP could be attenuated by the mGluR5 specific antagonist MPEP and the group II mGluR antagonist, MTPG (Cumiskey et al., 2007c) and also by the COX-2 inhibitor, SC-236, the iNOS inhibitor 1400W and peroxisome proliferation activated receptor (PPAR)γ agonist, ciglitazone (Cumiskey et al., 2007b). Interestingly IL-18 also inhibits LTP of C-fiber-evoked field potentials induced by tetanic stimulation of the sciatic nerve in the spinal cord and the authors identified a key role for microglial activation since IL-18 was localized largely to microglia and this effect was inhibited by minocycline (Chu et al., 2012).

Both IL-1β and IL-18 are processed by caspase 1, which is activated as a consequence of inflammasome activation. Assembly of the inflammasome, which is a collection of cytosolic proteins including pro-caspase 1, is triggered by activation of members of the mammalian nucleotide binding domain, leucine-rich repeat (LRR)-containing receptor (NLR) family and results in activation of caspase 1 with the subsequent processing and release of IL-1β and IL-18 (Tschopp et al., 2003; Walsh et al., 2014). Perhaps the most studied member of the family is NLRP3, which is present in microglia and plays a key role in regulating inflammation.

There are other NLR family members including NLRP1 and NLRP2, as well as 2 others, NLRC4 which contains an N-terminal caspase activation and recruitment domain (CARD), and absent in myeloma-2 (AIM2) (Walsh et al., 2014). NLRP1 and NLRP2 have been identified in neurons and astrocytes respectively (de Rivero Vaccari et al., 2014; Minkiewicz et al., 2013) although NLRP1 is also present in microglia, as is NLRC4 (Walsh et al., 2014). AIM2 has been identified in neurons (Walsh et al., 2014). Recent evidence has indicated that there is an age-related increase in NLRP1 activation (Mawhinney et al., 2011); the authors pointed out that this increase parallels the age-related increases in IL-1β and IL-18 although neurons are not the main producers of these

cytokines in the brain. The authors reported a correlation between NLRP1 activation and age-related impairment in spatial learning in Fischer 344 rats and demonstrated that probenecid, which inhibits pannexin-1 and therefore prevents inflammasome activity, improved spatial learning in older rats. A correlation between NLRP3 activation and synaptic plasticity has also been reported. We have reported that the ATP-induced $P2X_7$ inflammasome assembly in LPS-primed microglia was inhibited by a specific $P2X_7$ receptor antagonist, GSK1370319A, and that this antagonist improved the ability of aged rats to sustain LTP (Murphy et al., 2012). Since that report, it was shown that knockout of NLRP3 in transgenic mice that overexpress amyloid precursor protein and presenilin 1 (APP/PS1 mice) prevented the loss of LTP and poor spatial learning commonly observed in these animals (Heneka et al., 2013).

Other inflammatory cytokines also block LTP

In addition to IL-1β and IL-18, several other inflammatory cytokines also inhibit LTP, including type I and type II interferons (IFN). IFNα inhibited LTP in CA1 and this was attenuated by genistein indicating a role for tyrosine kinase in mediating the effect (Mendoza-Fernandez et al., 2000), while the inhibitory effect of IFNγ on LTP was attenuated by the phosphodiesterase inhibitor, ibudilast (Mizuno et al., 2004); it was suggested that this might be a consequence of the ibudilast-induced release of IL-10 and NGF from microglia. Intracerebroventricular injection of IFNγ also blocked LTP in perforant path-granule cell synapses of urethane-anaesthetized rats perhaps as a consequence of microglial activation and the associated increase in IL-1β (Maher et al., 2006), while the inhibitory effect of IFNγ on LTP in CA1 *in vitro* was also associated with increased IL-1β and microglial activation (Kelly et al., 2013).

Other inflammatory cytokines that have been reported to exert an inhibitory effect on LTP in hippocampus include IL-6 (Bellinger et al., 1995) and TNFα (Cowley et al., 2012; Cunningham et al., 1996; Wang et al., 2005), although TNFα (as well as IL-1β) also inhibits LTP in spinal cord lamina and the evidence suggested that the synaptic effects were mediated by TNFα- and IL-1β-induced stimulation of glia (Gruber-Schoffnegger et al., 2013). The inhibitory effect of TNFα, at least in vitro, appeared to rely on activation of the group I metabotropic glutamate receptor since it was blocked by the inhibitor, MCPG (Cumiskey et al., 2007a) although its effect was also associated with p38 MAP kinase activation (Butler et al., 2004). IL-2 (Tancredi et al., 1990) and IL-8 (Xiong et al., 2003) also exert an inhibitory effect on LTP.

Glial activation contributes to neuroinflammatory changes

The primary source of inflammatory cytokines in the brain is glia and both microglia and astrocytes can be stimulated to produce IL-1β, TNFα and IL-6 although astrocytes probably produce more IL-6 and less TNFα than microglia (Cowley et al., 2012; Minogue et al., 2012). There is unequivocal evidence that impairment in LTP is associated with evidence of microglial activation as indicated by increased expression of cell surface markers, which is indicative of their antigen presentation function, and upregulation of inflammatory cytokine expression (Lynch, 2009; Lynch, 2010). However in the past few years it has become clear that microglia are plastic cells and mimic macrophages in the sense that they respond to different stimuli by adopting different activation states.

Macrophages become classically-activated in response to IFNγ in vitro, adopting the so-called M1 phenotype; this phenotype is associated with increased production of inflammatory mediators and, in situ, is responsible for destruction of pathogens. In contrast, macrophages become alternatively-activated when incubated with anti-inflammatory

cytokines like IL-4 and adopt the so-called M2 activation state; these cells play a role in tissue repair (Gordon, 2003). Alternatively-activated cells were initially identified by Stein and colleagues when this group established that cells treated with anti-inflammatory cytokines failed to produce NO (an archetypal indicator of classically-activated cells), were not cytotoxic and did not exhibit antigen-presentation capability (Mosser, 2003; Stein et al., 1992). Like macrophages, microglia adopt the M1 phenotype when exposed to IFNγ or LPS and adopt the M2 phenotype when incubated in the presence of IL-4. The M1 microglia is identified by an increase in mRNA expression of TNFα and iNOS, whereas the M2 phenotype is identified by increased mRNA expression of arginase I, mannose receptor, chitinase 3-like 3 and found in inflammatory zone-1 (FIZZ1), although several other markers of the different phenotypes have been suggested (Chhor et al., 2013). In particular, the M1 phenotype is associated with increased expression of several inflammatory cytokines including IL-1β and IL-6 (Chhor et al., 2013; Colton and Wilcock, 2010) and also with increased expression of markers of oxidative stress (Colton and Wilcock, 2010) which negatively impacts on synaptic plasticity (Lynch, 2004). Indeed recent direct evidence has indicated that microglia in the brain of APP/PS1 mice, which exhibit a deficit in LTP (Kelly et al., 2013) adopt the M1 activation state (Minogue et al., 2014) and the same was true in CD200-deficient mice (Denieffe et al., 2013b) in which LTP is also decreased (Costello et al., 2011).

Switching microglial phenotypes and the impact on LTP

While factors which are associated with microglia adopting the M1 activation state, like IFNγ and LPS, are linked with a deficit in LTP, factors that switch microglia from the M1 to the M2 phenotype are associated with restoration of LTP or enhanced LTP. For instance, inhibiting IL-1β with a neutralising antibody resulted in macrophages adopting the M2 state (Mirza et al., 2013) and this is consistent with the ability of IL-1ra to attenuate the IL-1β-induced inhibition of LTP (Loscher et al., 2003). In contrast IL-4 and IL-10, which induce microglia to adopt the M2 phenotype (Chhor et al., 2013; Minogue et al., 2014), are capable of attenuating the impaired LTP which is characteristic of age and LPS treatment (Loane et al., 2009; Lynch et al., 2004; Nolan et al., 2005).

Perhaps predictably, Akt, which can be activated downstream of IL-4 receptor engagement, appears to play a role in controlling the switch between macrophage phenotypes (Arranz et al., 2012). Whereas increased activation of the PI3K/Akt pathway has been observed in LTP, inhibitors of this pathway block LTP (Bruel-Jungerman et al., 2009; Jo et al., 2011; Kelly and Lynch, 2000). A role for PPARγ in switching cells from an M1 to an M2 phenotype has been reported (Chawla, 2010; Mandrekar-Colucci et al., 2012), and it has been shown that rosiglitazone, the PPARγ activator, partially reversed the age-related deficit in LTP (Cowley et al., 2012; Loane et al., 2009) and it also attenuates the Aβ-induced inhibition of LTP (Costello et al., 2005). This may be as a consequences of its ability to increase hippocampal IL-4 concentration (Loane et al., 2009).

NADPH oxidase is perhaps the key enzyme responsible for production of reactive oxygen species and its activity is increased with age (Bruce-Keller et al., 2010; Kumar et al., 2013). Recent evidence suggests that inhibition of NADPH oxidase induces microglia to switch from the M1 to the M2 phenotype (Kumar et al., 2013) This is interesting since a loss of LTP has been associated with increased reactive oxygen species production induced by H_2O_2 (Vereker et al., 2001) or age (Murray and Lynch, 1998a) and that the age-related changes are attenuated by antioxidative strategies, namely lipoid acid and vitamins E and C (Lynch, 2001; McGahon et al., 1999; Murray and Lynch, 1998b).

One of the significant issues arising from the data that support the concept of microglia adopting the M1 phenotypes in vivo is identification of the cell source of IFNγ. The evidence indicates that resident brain cells do not produce significant amounts of the cytokine except in very specific circumstances (Suzuki et al., 2005) and that damage-associated molecular patterns (DAMPs), which also induce microglia to adopt the M1 phenotype, are produced only by dying cells. We have proposed that the source of IFNγ is infiltrating cells and report that Th1 cells, natural killer cells and macrophages infiltrate the brain of aged animals and APP/PS1 mice, release IFNγ and induce the microglia to adopt the M1 phenotype (Denieffe et al., 2013a; Kelly et al., 2013; Minogue et al., 2014). The evidence suggests that this cell infiltration is associated with increased blood brain barrier permeability. This raises the possibility that targetting the blood brain barrier might be a potentially useful therapeutic strategy in reducing neuroinflammatory changes that occur in the brain with age and neurodegenerative conditions.

Conclusions

There is little doubt that when microglia adopt the M1 phenotype and increase their production and release of inflammatory cytokines, synaptic plasticity is impaired. However careful analysis of the effect of IL-1β has revealed that the concentration of the cytokine determines the impact on LTP; specifically low concentrations and relatively acute exposure to IL-1β appears to be necessary for LTP whereas higher concentrations are detrimental. Whereas numerous factors have been shown to modulate the negative impact of inflammatory cytokines on LTP, significant clarity has developed as a result of a greater understanding of microglial phenotypes. Indeed the evidence to date indicates that factors which induce the M2 phenotype or switch M1 microglia into M2 microglia support LTP. This concept, which needs to be further assessed, may point to previously-unexplored mechanisms by which the compromised plasticity which develops with age and in models of Alzheimer's disease, might be reversed or limited.

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References

Arranz, A., Doxaki, C., Vergadi, E., Martinez de la Torre, Y., Vaporidi, K., Lagoudaki, E.D., Ieronymaki, E., Androulidaki, A., Venihaki, M., Margioris, A.N., Stathopoulos, E.N., Tsichlis, P.N., Tsatsanis, C., 2012. Akt1 and Akt2 protein kinases differentially contribute to macrophage polarization. Proc Natl Acad Sci U S A. 109**,** 9517-22.

Avital, A., Goshen, I., Kamsler, A., Segal, M., Iverfeldt, K., Richter-Levin, G., Yirmiya, R., 2003. Impaired interleukin-1 signaling is associated with deficits in hippocampal memory processes and neural plasticity. Hippocampus. 13**,** 826-34.

Barrientos, R.M., Higgins, E.A., Biedenkapp, J.C., Sprunger, D.B., Wright-Hardesty, K.J., Watkins, L.R., Rudy, J.W., Maier, S.F., 2006. Peripheral infection and aging interact to impair hippocampal memory consolidation. Neurobiol Aging. 27**,** 723-32.

Barrientos, R.M., Hein, A.M., Frank, M.G., Watkins, L.R., Maier, S.F., 2012. Intracisternal interleukin-1 receptor antagonist prevents postoperative cognitive decline and neuroinflammatory response in aged rats. J Neurosci. 32**,** 14641-8.

Barry, C.E., Nolan, Y., Clarke, R.M., Lynch, A., Lynch, M.A., 2005. Activation of c-Jun-N-terminal kinase is critical in mediating lipopolysaccharide-induced changes in the rat hippocampus. J Neurochem. 93**,** 221-31.

Bekinschtein, P., Oomen, C.A., Saksida, L.M., Bussey, T.J., 2011. Effects of environmental enrichment and voluntary exercise on neurogenesis, learning and memory, and pattern separation: BDNF as a critical variable? Semin Cell Dev Biol. 22**,** 536-42.

Bellinger, F.P., Madamba, S., Siggins, G.R., 1993. Interleukin 1 beta inhibits synaptic strength and long-term potentiation in the rat CA1 hippocampus. Brain Res. 628**,** 227-34.

Bellinger, F.P., Madamba, S.G., Campbell, I.L., Siggins, G.R., 1995. Reduced long-term potentiation in the dentate gyrus of transgenic mice with cerebral overexpression of interleukin-6. Neurosci Lett. 198**,** 95-8.

Ben Menachem-Zidon, O., Avital, A., Ben-Menahem, Y., Goshen, I., Kreisel, T., Shmueli, E.M., Segal, M., Ben Hur, T., Yirmiya, R., 2011. Astrocytes support hippocampal-dependent memory and long-term potentiation via interleukin-1 signaling. Brain Behav Immun. 25**,** 1008-16.

Blatteis, C.M., 1988. Neural mechanisms in the pyrogenic and acute-phase responses to interleukin-1. Int J Neurosci. 38**,** 223-32.

Bruce-Keller, A.J., White, C.L., Gupta, S., Knight, A.G., Pistell, P.J., Ingram, D.K., Morrison, C.D., Keller, J.N., 2010. NOX activity in brain aging: exacerbation by high fat diet. Free Radic Biol Med. 49**,** 22-30.

Bruel-Jungerman, E., Veyrac, A., Dufour, F., Horwood, J., Laroche, S., Davis, S., 2009. Inhibition of PI3K-Akt signaling blocks exercise-mediated enhancement of adult neurogenesis and synaptic plasticity in the dentate gyrus. PLoS One. 4**,** e7901.

Butler, M.P., O'Connor, J.J., Moynagh, P.N., 2004. Dissection of tumor-necrosis factor-alpha inhibition of long-term potentiation (LTP) reveals a p38 mitogen-activated protein kinase-dependent mechanism which maps to early-but not late-phase LTP. Neuroscience. 124**,** 319-26.

Chawla, A., 2010. Control of macrophage activation and function by PPARs. Circ Res. 106**,** 1559-69.

Chen, J., Buchanan, J.B., Sparkman, N.L., Godbout, J.P., Freund, G.G., Johnson, R.W., 2008. Neuroinflammation and disruption in working memory in aged mice after acute stimulation of the peripheral innate immune system. Brain Behav Immun. 22**,** 301-11.

Chhor, V., Le Charpentier, T., Lebon, S., Ore, M.V., Celador, I.L., Josserand, J., Degos, V., Jacotot, E., Hagberg, H., Savman, K., Mallard, C., Gressens, P., Fleiss, B., 2013. Characterization of phenotype markers and neuronotoxic potential of polarised primary microglia in vitro. Brain Behav Immun.

Chu, Y.X., Zhang, Y.Q., Zhao, Z.Q., 2012. Involvement of microglia and interleukin-18 in the induction of long-term potentiation of spinal nociceptive responses induced by tetanic sciatic stimulation. Neurosci Bull. 28**,** 49-60.

Clarke, R.M., O'Connell, F., Lyons, A., Lynch, M.A., 2007. The HMG-CoA reductase inhibitor, atorvastatin, attenuates the effects of acute administration of amyloid-beta1-42 in the rat hippocampus in vivo. Neuropharmacology. 52**,** 136-45.

Clarke, R.M., Lyons, A., O'Connell, F., Deighan, B.F., Barry, C.E., Anyakoha, N.G., Nicolaou, A., Lynch, M.A., 2008. A pivotal role for interleukin-4 in atorvastatin-associated neuroprotection in rat brain. J Biol Chem. 283**,** 1808-17.

Colton, C.A., Wilcock, D.M., 2010. Assessing activation states in microglia. CNS Neurol Disord Drug Targets. 9**,** 174-91.

Costello, D.A., O'Leary, D.M., Herron, C.E., 2005. Agonists of peroxisome proliferator-activated receptor-gamma attenuate the Abeta-mediated impairment of LTP in the hippocampus in vitro. Neuropharmacology. 49**,** 359-66.

Costello, D.A., Lyons, A., Denieffe, S., Browne, T.C., Cox, F.F., Lynch, M.A., 2011. Long term potentiation is impaired in membrane glycoprotein CD200-deficient mice: a role for Toll-like receptor activation. J Biol Chem. 286**,** 34722-32.

Cowley, T.R., O'Sullivan, J., Blau, C., Deighan, B.F., Jones, R., Kerskens, C., Richardson, J.C., Virley, D., Upton, N., Lynch, M.A., 2012. Rosiglitazone attenuates the age-related changes in astrocytosis and the deficit in LTP. Neurobiol Aging. 33**,** 162-75.

Cox, F.F., Carney, D., Miller, A.M., Lynch, M.A., 2012. CD200 fusion protein decreases microglial activation in the hippocampus of aged rats. Brain Behav Immun. 26**,** 789-96.

Cumiskey, D., Butler, M.P., Moynagh, P.N., O'Connor J, J., 2007a. Evidence for a role for the group I metabotropic glutamate receptor in the inhibitory effect of tumor necrosis factor-alpha on long-term potentiation. Brain Res. 1136**,** 13-9.

Cumiskey, D., Curran, B.P., Herron, C.E., O'Connor, J.J., 2007b. A role for inflammatory mediators in the IL-18 mediated attenuation of LTP in the rat dentate gyrus. Neuropharmacology. 52**,** 1616-23.

Cumiskey, D., Pickering, M., O'Connor, J.J., 2007c. Interleukin-18 mediated inhibition of LTP in the rat dentate gyrus is attenuated in the presence of mGluR antagonists. Neurosci Lett. 412**,** 206-10.

Cunningham, A.J., Murray, C.A., O'Neill, L.A., Lynch, M.A., O'Connor, J.J., 1996. Interleukin-1 beta (IL-1 beta) and tumour necrosis factor (TNF) inhibit long-term potentiation in the rat dentate gyrus in vitro. Neurosci Lett. 203**,** 17-20.

Curran, B., O'Connor, J.J., 2001. The pro-inflammatory cytokine interleukin-18 impairs long-term potentiation and NMDA receptor-mediated transmission in the rat hippocampus in vitro. Neuroscience. 108**,** 83-90.

Curran, B.P., Murray, H.J., O'Connor, J.J., 2003. A role for c-Jun N-terminal kinase in the inhibition of long-term potentiation by interleukin-1beta and long-term depression in the rat dentate gyrus in vitro. Neuroscience. 118**,** 347-57.

de Rivero Vaccari, J.P., Dietrich, W.D., Keane, R.W., 2014. Activation and regulation of cellular inflammasomes: gaps in our knowledge for central nervous system injury. J Cereb Blood Flow Metab. 34**,** 369-75.

Denieffe, S., Kelly, R.J., McDonald, C., Lyons, A., Lynch, M.A., 2013a. Classical activation of microglia in CD200-deficient mice is a consequence of blood brain barrier permeability and infiltration of peripheral cells. Brain Behavior and Immunity. 34**,** 86-97.

Denieffe, S., Kelly, R.J., McDonald, C., Lyons, A., Lynch, M.A., 2013b. Classical activation of microglia in CD200-deficient mice is a consequence of blood brain barrier permeability and infiltration of peripheral cells. Brain Behav Immun. 34**,** 86-97.

Dunne, A., O'Neill, L.A., 2003. The interleukin-1 receptor/Toll-like receptor superfamily: signal transduction during inflammation and host defense. Sci STKE. 2003**,** re3.

Eckert, M.J., Abraham, W.C., 2010. Physiological effects of enriched environment exposure and LTP induction in the hippocampus in vivo do not transfer faithfully to in vitro slices. Learn Mem. 17**,** 480-4.

Gallagher, J.J., Finnegan, M.E., Grehan, B., Dobson, J., Collingwood, J.F., Lynch, M.A., 2012. Modest Amyloid Deposition is Associated with Iron Dysregulation, Microglial Activation, and Oxidative Stress. J Alzheimers Dis. 28**,** 147-61.

Gallagher, J.J., Minogue, A.M., Lynch, M.A., 2013. Impaired Performance of Female APP/PS1 Mice in the Morris Water Maze Is Coupled with Increased Abeta Accumulation and Microglial Activation. Neurodegener Dis. 11**,** 33-41.

Godbout, J.P., Chen, J., Abraham, J., Richwine, A.F., Berg, B.M., Kelley, K.W., Johnson, R.W., 2005. Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. Faseb J. 19**,** 1329-31.

Gordon, S., 2003. Alternative activation of macrophages. Nat Rev Immunol. 3**,** 23-35.

Goshen, I., Kreisel, T., Ounallah-Saad, H., Renbaum, P., Zalzstein, Y., Ben-Hur, T., Levy-Lahad, E., Yirmiya, R., 2007. A dual role for interleukin-1 in hippocampal-dependent memory processes. Psychoneuroendocrinology. 32**,** 1106-15.

Goshen, I., Avital, A., Kreisel, T., Licht, T., Segal, M., Yirmiya, R., 2009. Environmental enrichment restores memory functioning in mice with impaired IL-1 signaling via reinstatement of long-term potentiation and spine size enlargement. J Neurosci. 29**,** 3395-403.

Griffin, R., Nally, R., Nolan, Y., McCartney, Y., Linden, J., Lynch, M.A., 2006. The age-related attenuation in long-term potentiation is associated with microglial activation. J Neurochem. 99**,** 1263-72.

Gruber-Schoffnegger, D., Drdla-Schutting, R., Honigsperger, C., Wunderbaldinger, G., Gassner, M., Sandkuhler, J., 2013. Induction of thermal hyperalgesia and synaptic long-term potentiation in the spinal cord lamina I by TNF-alpha and IL-1beta is mediated by glial cells. J Neurosci. 33**,** 6540-51.

Hayashi, Y., Yoshida, M., Yamato, M., Ide, T., Wu, Z., Ochi-Shindou, M., Kanki, T., Kang, D., Sunagawa, K., Tsutsui, H., Nakanishi, H., 2008. Reverse of age-dependent memory impairment and mitochondrial DNA damage in microglia by an overexpression of human mitochondrial transcription factor a in mice. J Neurosci. 28**,** 8624-34.

Hein, A.M., Stasko, M.R., Matousek, S.B., Scott-McKean, J.J., Maier, S.F., Olschowka, J.A., Costa, A.C., O'Banion, M.K., 2010. Sustained hippocampal IL-1beta overexpression impairs contextual and spatial memory in transgenic mice. Brain Behav Immun. 24**,** 243-53.

Hein, A.M., Zarcone, T.J., Parfitt, D.B., Matousek, S.B., Carbonari, D.M., Olschowka, J.A., O'Banion, M.K., 2012. Behavioral, structural and molecular changes following long-term hippocampal IL-1beta overexpression in transgenic mice. J Neuroimmune Pharmacol. 7**,** 145-55.

Heneka, M.T., Kummer, M.P., Stutz, A., Delekate, A., Schwartz, S., Vieira-Saecker, A., Griep, A., Axt, D., Remus, A., Tzeng, T.C., Gelpi, E., Halle, A., Korte, M., Latz, E., Golenbock, D.T., 2013. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature. 493**,** 674-8.

Iwai, T., Sawabe, T., Tanimitsu, K., Suzuki, M., Sasaki-Hamada, S., Oka, J., 2014. Glucagon-like peptide-1 protects synaptic and learning functions from neuroinflammation in rodents. J Neurosci Res. 92**,** 446-54.

Jo, J., Whitcomb, D.J., Olsen, K.M., Kerrigan, T.L., Lo, S.C., Bru-Mercier, G., Dickinson, B., Scullion, S., Sheng, M., Collingridge, G., Cho, K., 2011. Abeta(1-42) inhibition of LTP is mediated by a signaling pathway involving caspase-3, Akt1 and GSK-3beta. Nat Neurosci. 14**,** 545-7.

Katsuki, H., Nakai, S., Hirai, Y., Akaji, K., Kiso, Y., Satoh, M., 1990. Interleukin-1 beta inhibits long-term potentiation in the CA3 region of mouse hippocampal slices. Eur J Pharmacol. 181**,** 323-6.

Kelly, A., Lynch, M.A., 2000. Long-term potentiation in dentate gyrus of the rat is inhibited by the phosphoinositide 3-kinase inhibitor, wortmannin. Neuropharmacology. 39**,** 643-51.

Kelly, A., Lynch, A., Vereker, E., Nolan, Y., Queenan, P., Whittaker, E., O'Neill, L.A., Lynch, M.A., 2001. The anti-inflammatory cytokine, interleukin (IL)-10, blocks the inhibitory effect of IL-1 beta on long term potentiation. A role for JNK. J Biol Chem. 276**,** 45564-72.

Kelly, A., Vereker, E., Nolan, Y., Brady, M., Barry, C., Loscher, C.E., Mills, K.H., Lynch, M.A., 2003. Activation of p38 plays a pivotal role in the inhibitory effect of lipopolysaccharide and interleukin-1 beta on long term potentiation in rat dentate gyrus. J Biol Chem. 278**,** 19453-62.

Kelly, R.J., Minogue, A.M., Lyons, A., Jones, R.S., Browne, T.C., Costello, D.A., Denieffe, S., O'Sullivan, C., Connor, T.J., Lynch, M.A., 2013. Glial Activation in A beta PP/PS1 Mice is Associated with Infiltration of IFN gamma-Producing Cells. Journal of Alzheimers Disease. 37**,** 63-75.

Kitazawa, M., Cheng, D., Tsukamoto, M.R., Koike, M.A., Wes, P.D., Vasilevko, V., Cribbs, D.H., LaFerla, F.M., 2011. Blocking IL-1 signaling rescues cognition, attenuates tau pathology, and restores neuronal beta-catenin pathway function in an Alzheimer's disease model. J Immunol. 187**,** 6539-49.

Kluger, M.J., 1991. Fever: role of pyrogens and cryogens. Physiol Rev. 71**,** 93-127.

Kumar, A., Stoica, B.A., Sabirzhanov, B., Burns, M.P., Faden, A.I., Loane, D.J., 2013. Traumatic brain injury in aged animals increases lesion size and chronically alters microglial/macrophage classical and alternative activation states. Neurobiol Aging. 34**,** 1397-411.

Lante, F., Meunier, J., Guiramand, J., De Jesus Ferreira, M.C., Cambonie, G., Aimar, R., Cohen-Solal, C., Maurice, T., Vignes, M., Barbanel, G., 2008. Late N-acetylcysteine treatment prevents the deficits induced in the offspring of dams exposed to an immune stress during gestation. Hippocampus. 18**,** 602-9.

Liu, X., Wu, Z., Hayashi, Y., Nakanishi, H., 2012. Age-dependent neuroinflammatory responses and deficits in long-term potentiation in the hippocampus during systemic inflammation. Neuroscience. 216**,** 133-42.

Loane, D.J., Deighan, B.F., Clarke, R.M., Griffin, R.J., Lynch, A.M., Lynch, M.A., 2009. Interleukin-4 mediates the neuroprotective effects of rosiglitazone in the aged brain. Neurobiol Aging. 30**,** 920-31.

Lonergan, P.E., Martin, D.S., Horrobin, D.F., Lynch, M.A., 2002. Neuroprotective effect of eicosapentaenoic acid in hippocampus of rats exposed to gamma-irradiation. J Biol Chem. 277**,** 20804-11.

Loscher, C.E., Mills, K.H., Lynch, M.A., 2003. Interleukin-1 receptor antagonist exerts agonist activity in the hippocampus independent of the interleukin-1 type I receptor. J Neuroimmunol. 137**,** 117-124.

Lynch, A.M., Walsh, C., Delaney, A., Nolan, Y., Campbell, V.A., Lynch, M.A., 2004. Lipopolysaccharide-induced increase in signalling in hippocampus is abrogated by IL-10--a role for IL-1 beta? J Neurochem. 88**,** 635-46.

Lynch, A.M., Loane, D.J., Minogue, A.M., Clarke, R.M., Kilroy, D., Nally, R.E., Roche, O.J., O'Connell, F., Lynch, M.A., 2007. Eicosapentaenoic acid confers neuroprotection in the amyloid-beta challenged aged hippocampus. Neurobiol Aging. 28**,** 845-55.

Lynch, M.A., 1998. Age-related impairment in long-term potentiation in hippocampus: a role for the cytokine, interleukin-1 beta? Prog Neurobiol. 56**,** 571-89.
Lynch, M.A., 2001. Lipoic acid confers protection against oxidative injury in non-neuronal and neuronal tissue. Nutr Neurosci. 4**,** 419-38.
Lynch, M.A., 2004. Long-term potentiation and memory. Physiol Rev. 84**,** 87-136.
Lynch, M.A., 2009. The multifaceted profile of activated microglia. Mol Neurobiol. 40**,** 139-56.
Lynch, M.A., 2010. Age-related neuroinflammatory changes negatively impact on neuronal function. Front Aging Neurosci. 1**,** 6.
Lyons, A., Griffin, R.J., Costelloe, C.E., Clarke, R.M., Lynch, M.A., 2007. IL-4 attenuates the neuroinflammation induced by amyloid-beta in vivo and in vitro. J Neurochem. 101**,** 771-81.
Maggio, N., Shavit-Stein, E., Dori, A., Blatt, I., Chapman, J., 2013. Prolonged systemic inflammation persistently modifies synaptic plasticity in the hippocampus: modulation by the stress hormones. Front Mol Neurosci. 6**,** 46.
Maher, F.O., Clarke, R.M., Kelly, A., Nally, R.E., Lynch, M.A., 2006. Interaction between interferon gamma and insulin-like growth factor-1 in hippocampus impacts on the ability of rats to sustain long-term potentiation. J Neurochem. 96**,** 1560-71.
Mandrekar-Colucci, S., Karlo, J.C., Landreth, G.E., 2012. Mechanisms Underlying the Rapid Peroxisome Proliferator-Activated Receptor-gamma-Mediated Amyloid Clearance and Reversal of Cognitive Deficits in a Murine Model of Alzheimer's Disease. J Neurosci. 32**,** 10117-28.
Mawhinney, L.J., de Rivero Vaccari, J.P., Dale, G.A., Keane, R.W., Bramlett, H.M., 2011. Heightened inflammasome activation is linked to age-related cognitive impairment in Fischer 344 rats. BMC Neurosci. 12**,** 123.
McGahon, B.M., Martin, D.S., Horrobin, D.F., Lynch, M.A., 1999. Age-related changes in LTP and antioxidant defenses are reversed by an alpha-lipoic acid-enriched diet. Neurobiol Aging. 20**,** 655-64.
Mendoza-Fernandez, V., Andrew, R.D., Barajas-Lopez, C., 2000. Interferon-alpha inhibits long-term potentiation and unmasks a long-term depression in the rat hippocampus. Brain Res. 885**,** 14-24.
Minkiewicz, J., de Rivero Vaccari, J.P., Keane, R.W., 2013. Human astrocytes express a novel NLRP2 inflammasome. Glia. 61**,** 1113-21.
Minogue, A.M., Barrett, J.P., Lynch, M.A., 2012. LPS-induced release of IL-6 from glia modulates production of IL-1 beta in a JAK2-dependent manner. J Neuroinflammation. 9**,** 126.
Minogue, A.M., Jones, R.S., Kelly, R.J., McDonald, C.L., Connor, T.J., Lynch, M.A., 2014. Age-associated dysregulation of microglial activation is coupled with enhanced blood-brain barrier permeability and pathology in APP/PS1 mice. Neurobiol Aging. 35**,** 1442-52.
Mirza, R.E., Fang, M.M., Ennis, W.J., Koh, T.J., 2013. Blocking interleukin-1beta induces a healing-associated wound macrophage phenotype and improves healing in type 2 diabetes. Diabetes. 62**,** 2579-87.
Mizuno, T., Kurotani, T., Komatsu, Y., Kawanokuchi, J., Kato, H., Mitsuma, N., Suzumura, A., 2004. Neuroprotective role of phosphodiesterase inhibitor ibudilast on neuronal cell death induced by activated microglia. Neuropharmacology. 46**,** 404-11.
Mosser, D.M., 2003. The many faces of macrophage activation. J Leukoc Biol. 73**,** 209-12.

Murphy, N., Cowley, T.R., Richardson, J.C., Virley, D., Upton, N., Walter, D., Lynch, M.A., 2012. The neuroprotective effect of a specific P2X(7) receptor antagonist derives from its ability to inhibit assembly of the NLRP3 inflammasome in glial cells. Brain Pathol. 22**,** 295-306.

Murray, C.A., Lynch, M.A., 1998a. Evidence that increased hippocampal expression of the cytokine interleukin-1 beta is a common trigger for age- and stress-induced impairments in long-term potentiation. J Neurosci. 18**,** 2974-81.

Murray, C.A., Lynch, M.A., 1998b. Dietary supplementation with vitamin E reverses the age-related deficit in long term potentiation in dentate gyrus. J Biol Chem. 273**,** 12161-8.

Nolan, Y., Maher, F.O., Martin, D.S., Clarke, R.M., Brady, M.T., Bolton, A.E., Mills, K.H., Lynch, M.A., 2005. Role of interleukin-4 in regulation of age-related inflammatory changes in the hippocampus. J Biol.Chem. 280**,** 9354-9362.

Ross, F.M., Allan, S.M., Rothwell, N.J., Verkhratsky, A., 2003. A dual role for interleukin-1 in LTP in mouse hippocampal slices. J Neuroimmunol. 144**,** 61-7.

Schneider, H., Pitossi, F., Balschun, D., Wagner, A., del Rey, A., Besedovsky, H.O., 1998. A neuromodulatory role of interleukin-1beta in the hippocampus. Proc Natl Acad Sci U S A. 95**,** 7778-83.

Shaw, K.N., Commins, S., O'Mara, S.M., 2001. Lipopolysaccharide causes deficits in spatial learning in the watermaze but not in BDNF expression in the rat dentate gyrus. Behav Brain Res. 124**,** 47-54.

Spulber, S., Bartfai, T., Schultzberg, M., 2009. IL-1/IL-1ra balance in the brain revisited - evidence from transgenic mouse models. Brain Behav Immun. 23**,** 573-9.

Stein, M., Keshav, S., Harris, N., Gordon, S., 1992. Interleukin 4 potently enhances murine macrophage mannose receptor activity: a marker of alternative immunologic macrophage activation. J Exp Med. 176**,** 287-92.

Suzuki, Y., Claflin, J., Wang, X., Lengi, A., Kikuchi, T., 2005. Microglia and macrophages as innate producers of interferon-gamma in the brain following infection with Toxoplasma gondii. Int J Parasitol. 35**,** 83-90.

Tancredi, V., Zona, C., Velotti, F., Eusebi, F., Santoni, A., 1990. Interleukin-2 suppresses established long-term potentiation and inhibits its induction in the rat hippocampus. Brain Res. 525**,** 149-51.

Tong, L., Prieto, G.A., Kramar, E.A., Smith, E.D., Cribbs, D.H., Lynch, G., Cotman, C.W., 2012. Brain-derived neurotrophic factor-dependent synaptic plasticity is suppressed by interleukin-1beta via p38 mitogen-activated protein kinase. J Neurosci. 32**,** 17714-24.

Tschopp, J., Martinon, F., Burns, K., 2003. NALPs: A novel protein family involved in inflammation. Nature Reviews Molecular Cell Biology. 4**,** 95-104.

Vereker, E., Campbell, V., Roche, E., McEntee, E., Lynch, M.A., 2000a. Lipopolysaccharide inhibits long term potentiation in the rat dentate gyrus by activating caspase-1. J Biol Chem. 275**,** 26252-8.

Vereker, E., O'Donnell, E., Lynch, M.A., 2000b. The inhibitory effect of interleukin-1beta on long-term potentiation is coupled with increased activity of stress-activated protein kinases. J Neurosci. 20**,** 6811-9.

Vereker, E., O'Donnell, E., Lynch, A., Kelly, A., Nolan, Y., Lynch, M.A., 2001. Evidence that interleukin-1beta and reactive oxygen species production play a pivotal role in stress-induced impairment of LTP in the rat dentate gyrus. Eur J Neurosci. 14**,** 1809-19.

Walsh, J.G., Muruve, D.A., Power, C., 2014. Inflammasomes in the CNS. Nat Rev Neurosci. 15**,** 84-97.

Wang, Q., Wu, J., Rowan, M.J., Anwyl, R., 2005. Beta-amyloid inhibition of long-term potentiation is mediated via tumor necrosis factor. Eur J Neurosci. 22**,** 2827-32.

Xiong, H., Boyle, J., Winkelbauer, M., Gorantla, S., Zheng, J., Ghorpade, A., Persidsky, Y., Carlson, K.A., Gendelman, H.E., 2003. Inhibition of long-term potentiation by interleukin-8: implications for human immunodeficiency virus-1-associated dementia. J Neurosci Res. 71**,** 600-7.