How dependent is synaptic plasticity on microglial phenotype?

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Abstract

Microglia are particularly plastic cells which can be shifted from their resting state by numerous factors and adopt distinct phenotypes. The cells are multifunctional, though their main role is probably maintenance of homeostasis. Resting cells are responsible for surveillance, whereas activation induces the cells to adopt neuroprotective or neurodetrimental roles, which are anti-inflammatory or pro-inflammatory respectively. The evidence indicates that activated cells with a pro-inflammatory phenotype predominate in neurodegenerative diseases and models of neurodegeneration and that this may significantly contribute to the deteriorating neuronal function. This question is considered in this review, in particular in the context of animal models of Alzheimer's disease (AD).

Highlights

- IFNγ and TNFα induce microglia to adopt a classically-activated, or M1, phenotype
- IL-4 and IL-13 induce the alternatively-activated, or M2, phenotype
- M1 activation is associated with impaired synaptic function and neurodegeneration
- Aβ, microglial activation and impaired LTP are features in animal models of AD
- The driving force behind these changes remains to be elucidated

Keywords:
Neuroinflammation, Microglia, Astrocytes, Inflammatory cytokines, Age, Alzheimer's disease, Neuronal function.

1. Introduction

The idea that microglia are 'the macrophages of the brain', although inaccurate, is useful when considering their phenotypes since there is a great deal more understanding of the biology of macrophages. However, while macrophages and microglia are cells of the myeloid lineage, microglia are derived from primitive macrophages in the yolk sac that migrate to the central nervous system (CNS) early in development (Ginhoux *et al*., 2010). Therefore, a fundamental difference between the cells is that they encounter entirely diverse stimuli throughout life; for example, microglia are juxtaposed with cells that are electrically active, while macrophages are exposed to a wide variety of pathogens that, in the main, do not pass the blood brain barrier and therefore are generally not encountered by microglia.

Microglia, as sentinel cells in the brain, react to any stimulus that poses a potential threat to the brain. Indeed activation of glia, especially microglia, is fundamentally responsible for the inflammatory changes that characterize the brain following exposure to any insult. For example, ischemia, injury and infection are associated with rapid microglial activation and associated inflammatory changes, but these are designed to combat the effect of the insult and ultimately return the tissue to homeostasis. This acute reaction is therefore considered to be protective. In contrast, persistent microglial activation with the associated increase in expression of inflammatory cytokines and chemokines, accompanied by recruitment of peripheral cells into the brain, characterizes chronic neuroinflammation (Lynch, 2009, 2010). It has been known for many years that neuroinflammatory changes are a characteristic of, and persist in, the brain of aged individuals and a great deal of data suggests that neuroinflammation is one of the common features of several neurodegenerative diseases (Akiyama *et al*., 2000; Lynch, 2013). As reviewed by several authors, microglial activation has been described in Alzheimer's disease (AD) (Fuller *et al*., 2009; Heneka and O'Banion, 2007; McGeer and McGeer, 2003), Parkinson's disease (PD) (Long-Smith *et al*., 2009; McGeer and McGeer, 2008; Ouchi *et al*., 2009) and indeed there is epidemiological evidence indicating that anti-inflammatory agents reduce the risk of AD (Launer, 2003; Rich *et al*., 1995; Vlad *et al*., 2008) and PD (Chen *et al*., 2005; Esposito *et al*., 2007).

It has become increasingly clear that to categorize microglia as resting or activated is simplistic, since the cells express a diverse array of receptors and therefore respond to an equally diverse array of ligands. Current evidence indicates that, like macrophages, microglia react differently to various stimuli. It is also simplistic to consider that microglia are a homogenous population of cells and emerging evidence indicates that there are probably regional differences. Microglia are unevenly distributed in the brain; in the mouse brain, microglial numbers are greater in grey matter than in white matter (Lawson *et al*., 1990), but the opposite has been reported in human brain (Mittelbronn *et al*., 2001). With respect to anatomical areas, overall microglial numbers are amongst the lowest in cerebellum of both mouse and human brain and highest in hippocampus of the mouse and medulla oblongata of the human (Lawson *et al*., 1990; Mittelbronn *et al*., 2001). Interestingly, phenotypic differences have been observed in unstimulated microglial cultures prepared from different brain regions, with higher mRNA expression of tumour necrosis factor alpha (TNFα), Fc gamma receptor and CD4 in microglia from hippocampus than other regions studied, including cortex and cerebellum (Ren *et al*., 1999). This, and other findings, raise the possibility that resting state microglia are a heterogeneous population with subgroups of microglia assigned specific 'house-keeping' functions, as so eloquently discussed in a recent review (Hanisch, 2013). The heterogeneity of microglia becomes more evident when cells shift from their resting state; for example, age-related changes in expression of different markers of microglial activation were found to be region-specific with the most profound changes in CD11b, CD68 and F4/80 observed in the cerebellum (Hart *et al*., 2012).

2. Microglial activation

2.1. Resting microglia

The primary role of microglia under resting conditions is maintenance of homeostasis, neuroprotection and neurorepair, and repair, at least, is probably dependent on release of growth factors such as brain-derived neurotrophic factor (BDNF) and transforming growth factor (TGF)β (Morgan *et al*., 2004). Time-lapse transcranial imaging of resting microglia showed that protrusion and retraction of processes is transient and occurs with high turnover. These processes make contact with astrocytes, neurons and blood vessels and sample the parenchyma every few hours. Tissue insult results in rapid recruitment of adjacent microglia and the appearance of spherical protrusions on their retracted processes, which is indicative of phagocytosis (Nimmerjahn *et al*., 2005). Interestingly, microglial interaction with presynaptic terminals and dendritic spines is dependent on neuronal activity (Wake *et al*., 2009).

2.1.1. What factors contribute to the maintenance of microglia in a resting state?

Resting microglia constitutively express surface receptors including complement receptors, Fc and CD4, and also CD200 and fractalkine receptors (CX3CR1) which are described as 'off signals' by Biber and colleagues in their review; these receptors engage with their respective ligands and help to maintain microglia in a quiescent state (Biber *et al*., 2007). Whereas CD200 is widely distributed, CD200 receptor expression is confined to cells of the myeloid lineage; consequently co-culturing of neurons with microglia decreases lipopolysaccharide (LPS)- or amyloid-β (Aβ)-induced microglial activation and this is dependent on interaction of CD200 with its receptor (Lyons *et al*., 2007a; Lyons *et al*., 2009b). The largely complementary expression of fractalkine on neurons and its receptor on microglia (Harrison *et al*., 1998) suggests an interaction similar to that described for CD200-CD200R, and evidence to support this has been reported (Cardona *et al*., 2006; Lyons *et al*., 2009a). CD45 and signal regulatory protein (SIRP)1α, which are expressed predominantly on microglia, interact with neuronally expressed CD22 and CD47 respectively (Biber *et al*., 2007; Mott *et al*., 2004). These interactions appear to function as 'off' signals as do secreted CD22 and fractalkine (Biber *et al*., 2007), neurotrophins and anti-inflammatory cytokines such as interleukin (IL)-10 and IL-4 (Biber *et al*., 2007; Lyons *et al*., 2007b). These factors attenuate changes induced in microglia by stimuli that include interferon-γ (IFNγ), LPS and Aβ (Clarke *et al*., 2008; Lyons *et al*., 2007b) and, interestingly, age-related decreases in expression of several of these 'off ' signals have been reported (Lyons *et al*., 2009a; Moore *et al*., 2007; Nolan *et al*., 2005).

2.2. The shift of microglia from their non-resting state and markers of activation

Activated microglia typically upregulate expression of cell surface markers such as major histocompatibility complex (MHC) II and co-stimulatory molecules including CD80 and CD86 (Bhatia *et al*., 2006; Greenwald *et al*., 2005; Wolf *et al*., 2001), which enable microglia to interact with T cells and function as antigen presenting cells (APC). In addition, CD40 and CD11b, which are constitutively expressed on microglia, are upregulated upon activation (Nguyen and Benveniste, 2000; Qin *et al*., 2005; Streit *et al*., 1999; Tan *et al*., 2002); these contribute to activation and re-stimulation of T cells (Benveniste *et al*., 2004), production of inflammatory cytokines (Chen *et al*., 2006), cell motility, cell-mediated cytotoxicity and chemotaxis (Nagai *et al*., 2005; Solovjov *et al*., 2005; Weber *et al*., 1997), whereas upregulation of intercellular adhesion molecule (ICAM)-1 correlates with blood brain barrier permeability and leukocyte infiltration (Corti *et al*., 2004; Zameer and Hoffman, 2003). It has been repeatedly shown that increased expression of these markers of microglial activation is associated with impaired neuronal/synaptic function and therefore

with deficits in different types of learning and memory and in the archetypal form of synaptic plasticity, long-term potentiation (LTP); for example, this relationship has been reported following treatment of animals with LPS or Aβ and in aged animals (Clarke *et al*., 2008; Cowley *et al*., 2012; Lynch *et al*., 2007; Lynch, 2010).

2.2.1. Microglia adopt different phenotypes in response to different stimuli

It has been known for a few decades that macrophages adopt different activation states, identified by upregulation of specific markers, in response to diverse signals and this has been comprehensively reviewed (Gordon, 2003; Mosser, 2003). The activation states are broadly described as the classically-activated, or M1, phenotype and the alternatively-activated, or M2, phenotype. Typically the Th1 cell-derived cytokine IFNγ induces the M1 phenotype, which is identified by increased mRNA expression of TNFα and inducible nitric oxide synthase (iNOS). The term alternative activation (M2a phenotype) was first used to describe a macrophage which adopted a phenotype distinct from that induced by IFNγ and LPS (Stein *et al*., 1992). These cells were not capable of producing nitric oxide (NO) and so were not cytotoxic and, although MHCII expression was increased, the cells were not efficient APC and prevented proliferation of T cells (Mosser, 2003). This phenotype is induced by the Th2 cell-derived cytokines, IL-4, IL-5 a nd IL-13 and is identified by increased mRNA expression of arginase 1, mannose receptor, chitinase 3-like 3 and found in inflammatory zone (FIZZ)-1. Two further M2 phenotypes have been described; the acquired deactivated (M2c) phenotype is induced by the immunosuppressive cytokines, IL-10 and TGFβ, and is associated with upregulation of anti-inflammatory cytokines and downregulation of factors that contribute to APC function such as MHCII, whereas the immunoregulatory M2b phenotype is induced by a number of factors including immune complexes (Gordon, 2003). A recent comprehensive study revealed that, broadly, these phenotypes could be identified in cultured microglia (Chhor *et al*., 2013). Table 1 summarizes the characteristics of M1 and M2 phenotypes.

A significant issue relates to the nature of the stimuli that might trigger classical and alternative activation states in microglia *in vivo* since resident cells in the brain produce limited IFNγ and IL-4. One possibility is that infiltrating cells are responsible for production of these cytokines and, consequently, for triggering polarization of microglia into classically- and alternatively-activated phenotypes. Increased expression of markers of M1 microglia have been correlated with evidence of infiltrating IFNγ-producing T cells and NK cells in the brain of aged animals and in transgenic mice that overexpress amyloid precursor protein (APP) and presenilin 1 (PS1; APP/PS1 mice), a commonly used animal model of AD (Kelly *et al*., 2013b; McManus *et al*., 2014; Minogue *et al*., 2014). A second possibility is that other polarizing stimuli substitute for IFNγ and IL-4 in the brain. LPS induces many characteristics of the M1 phenotype and therefore endogenously-produced toll-like receptor (TLR)4 ligands may provide the activation signal *in vivo*.

It seems that acute activation of microglia, leading to the M1 activation state, is protective, at least in ischaemia, as recently reviewed (Cherry *et al*., 2014), with the primary aim of the cells being to eliminate or neutralize the stressor that initiated the event. When this is achieved, it is believed that the cells return to their resting state, perhaps having transiently adopted the M2 activation state, to ensure tissue repair and restoration of function as reviewed by others (Cherry *et al*., 2014; Colton and Wilcock, 2010). However, it is believed that chronic activation of microglia is damaging to tissue and the evidence suggests that this occurs with age and, to a significant extent, in neurodegenerative diseases as recently reviewed (Cherry *et al*., 2014).

Table 1. Microglial phenotypes and characteristics

Phenotype/Role		Activating stimuli	Primary phenotypic markers	Cytokines produced
M1	• Classical activation • Protection against insult	IFNγ, LPS, TNFα	iNOS, TNFα, MHCII, CD86	Inflammatory cytokines e.g. IL-12, IL-1β, IL-6, IL-2
M2a	• Initially identified as distinct from classically-activated state and termed alternative activation • Repair, anti-inflammatory	IL-4, IL-13	Mannose receptor, arginase 1, FIZZ-1, chitinase 3-like 3, chemokines and receptors including CX3CR1, CCL2, CCR2	IL-10, IL-1ra, TGFβ
M2b	• Modulatory/ regulatory phenotype	Immune complexes	IL-10, cyclooxygenase (COX)2, sphingosine kinase, suppressor of cytokine signaling (SOCS)3	IL-1β, IL-6, IL-10, TNFα
M2c	• Acquired, deactivated state • Anti-inflammatory	IL-10, TGFβ	CD163	IL-10, TGFβ

2.3. Microglial activation is associated with decreased LTP

The importance of microglial activation in modulating neuronal function, particularly hippocampal function, has been recognized for decades since the first observations that IL-1β (and latterly other inflammatory cytokines), 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). Indeed these reports post-date the recognition that IL-1β exerts an inhibitory effect on LTP in CA1 (Bellinger *et al*., 1993), CA3 (Katsuki *et al*., 1990) and dentate gyrus *in vitro* (Cunningham *et al*., 1996). These reports were followed by several others indicating similar inhibitory effects of IL-1β on LTP *in vivo* (Murray and Lynch, 1998), and the acknowledgement that the inhibitory effect of LPS and age on LTP may be a consequence of increased hippocampal expression of IL-1β (Murray and Lynch, 1998).

2.3.1. What is the basis of the inverse correlation between microglial activation and the deficit in LTP?

The most parsimonious explanation for the negative impact of Aβ, LPS and age on LTP is that activated microglia release inflammatory mediators, including pro-inflammatory cytokines such as IL-1β, IL-6 and TNFα, which have been known for many years to impair LTP *in vivo* and *in vitro* as reviewed previously (Lynch, 2010); the extent of the change in LTP varies with preparation (*in vivo* vs *in vitro*), concentration and cytokine, although in most cases, induction of LTP is spared. Additionally, potent activators of microglia e.g. IFNγ, which induces release of inflammatory cytokines from microglia, also inhibit LTP (Kelly *et al*., 2013a) and interestingly this effect is blocked by the anti-inflammatory cytokine, IL-4 (Maher *et al*., 2006).

The age-related increase in microglial activation, as indicated by expression of markers such as MHCII and CD68, appears to confer a susceptibility to inflammatory

stimuli such that their effects on aged animals are more marked than on young animals. Specifically, an increase in production of inflammatory cytokines is reported to be coupled with deficits in hippocampal-dependent learning tasks (Barrientos *et al*., 2006; Chen *et al*., 2008) and enhanced microglial activation (Lynch *et al*., 2010). Aβ also induces a greater negative effect on LTP in aged, compared with young, rats and this is associated with an age-related increase in the effect of Aβ on IL-1β concentration in the hippocampus (Lynch *et al*., 2007).

2.3.2. Is there a link between astrocytic activation and LTP?

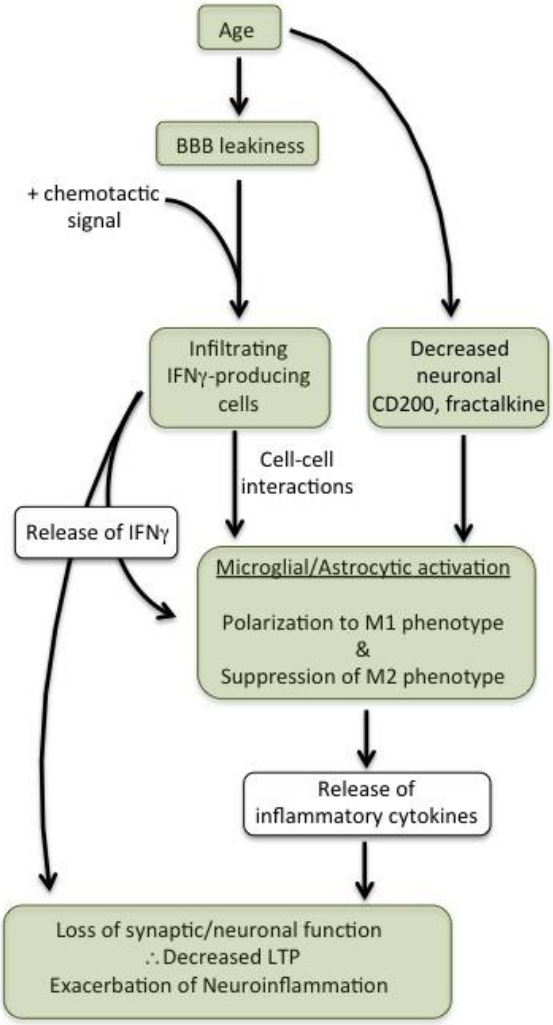
Microglial activation is often accompanied by that of astrocytes, for example in aged animals and APP/PS1 mice (Cowley *et al*., 2012; Gallagher *et al*., 2012; Gallagher *et al*., 2013; Kelly *et al*., 2013a) and astrocytes, like microglia, release inflammatory cytokines (Cowley *et al*., 2012). Therefore, while there is a particularly strong link between microglial activation and LTP, the potential impact of astrocytic activation on LTP cannot be ignored. Indeed the critical role of astrocytes in controlling extracellular concentrations of neurotransmitters such as glutamate and GABA, as well as purines, by regulated uptake and release has been well described (Halassa *et al*., 2007) and these factors impact on LTP. Additionally, astrocytes modulate microglial activation. One possibility is that this may derive from the fact that astrocytes can release GABA, which activates GABA receptors expressed by microglia (Lee *et al*., 2011). It is clear that astrocytes can also release inflammatory factors that trigger microglial activation and therefore contribute to the changes that occur as a consequence of chronic inflammation (Pascual *et al*., 2012; von Bernhardi and Ramirez, 2001). On the other hand, astrocytes secrete soluble factors including growth factors and anti-inflammatory cytokines (Eng *et al*., 2000) that decrease microglial activation. It has been shown that conditioned medium obtained from astrocytes decreased hydrogen peroxide (H_2O_2)-induced reactive oxygen species (ROS) production, increased expression and activity of the antioxidant enzyme, haemoxygenase-1, and decreased IFNγ-induced inducible iNOS expression in microglia (Min *et al*., 2006). Astrocytes also modulate microglial activation by virtue of the fact that they express CD200 (Cox *et al*., 2013); indeed incubation of microglia with CD200-bearing astrocytic membrane preparations attenuates the LPS-induced increase in mRNA expression of IL-1β, TNFα and IL-6 and the LPS-induced release of TNFα and IL-6 (Cox *et al*., 2013).

2.3.3. Loss of 'off signals' is associated with microglial activation and deficits in LTP

The inverse relationship between microglial activation and synaptic plasticity has been linked with a decrease in expression of 'off' signals. For example, decreased expression of CD200, which occurs with age or following Aβ treatment (Lyons *et al*., 2007a), is associated with a poorer ability of animals to sustain LTP, and slices prepared from mice lacking CD200 also exhibit a deficit in LTP (Costello *et al*., 2011). Interestingly, the deficit in LTP in aged animals is attenuated by CD200Fc (Cox *et al*., 2012), whereas both the age-related and Aβ-induced decrease in LTP is at least partially reversed by IL-4 (Lyons *et al*., 2007b; Nolan *et al*., 2005), which increases hippocampal expression of CD200 (Lyons *et al*., 2009b). The age-related deficit in LTP and accompanying increase in microglial activation, are also associated with decreased hippocampal expression of fractalkine (Lyons *et al*., 2009a) and IL-10 (Moore *et al*., 2007). The relationship between neuroinflammation, particularly microglial activation, and impaired LTP, has been consolidated by the finding that strategies which attenuate microglial activation, including polyunsaturated fatty acids, statins or anti-inflammatory cytokines, also attenuate the loss of LTP (Adams *et al*., 1998); this is the case in a number of models in which LTP is decreased including in Aβ- and LPS-treated animals and in aged animals (Clarke *et al*., 2008; Clarke *et al*., 2007; Cowley *et al*.,

2012; Kelly *et al*., 2001; Kelly *et al*., 2011; Nolan *et al*., 2005). Figure 1 summarizes the factors that contribute to the age-related attenuation of LTP.

Figure 1. Proposed sequence leading to age-related decrease in LTP



Age is associated with increased blood brain barrier permeability which, together with a chemotactic signal, increases infiltration of peripheral cells. These include NK and Th1 cells, which produce IFNγ, and this has a negative impact on LTP but also induces microglia, and probably astrocytes, to adopt the inflammatory M1 phenotype. These cells consequently increase production of inflammatory cytokines and reactive oxygen and nitrogen species which results in a loss of synaptic function and therefore LTP, while contributing to the existing neuroinflammation. In addition, age is associated with decreased expression of neuromodulatory molecules such as CD200 and fractalkine, which contribute to the maintenance of microglia in a quiescent state. This loss of control on microglia also permits increased production of inflammatory cytokines. It is proposed that a similar sequence of events occurs in models of Alzheimer's disease.

3. Microglial activation, Aβ and LTP

3.1. Aβ inhibits LTP

The ability of Aβ to induce microglial activation (Combs *et al*., 2001; Lyons *et al*., 2007b) and increase the expression and release of IL-1β and TNFα from microglia (Lyons *et al*., 2012; McQuillan *et al*., 2010) is well-documented. This might suggest that inflammatory changes are Aβ-driven (Hensley, 2010), although this linear model is confounded by the finding that inflammatory cytokines increase APP processing (Blasko *et al*., 2000; Zhao *et al*., 2011).

Several authors have reported that different forms of Aβ have the capacity to inhibit LTP *in vivo* and *in vitro*. One of the earliest papers reported that central administration of Aβ inhibited LTP in area CA1 of the hippocampus (Cullen *et al*., 1997) and this observation was followed by several others which indicated that synthetic and naturally-occurring Aβ oligomers, including Aβ-derived diffusible ligands, inhibited LTP in all major afferent pathways in the hippocampus both *in vivo* and *in vitro* (Koffie *et al*., 2011; Ondrejcak *et al*., 2010; Walsh *et al*., 2002).

Although several groups have reported that acute Aβ treatment inhibits LTP (Freir *et al*., 2001; Klyubin *et al*., 2004; Minogue *et al*., 2003; Walsh *et al*., 2002), fewer have examined the impact of chronic Aβ perfusion. However, it has been shown that LTP was decreased in CA1 in slices prepared from rats treated with Aβ for 10 days (Itoh *et al*., 1999). Unpublished data from this laboratory have demonstrated that intracerebroventricular administration of $A\beta_{1\text{-}40}$ + $A\beta_{1\text{-}42}$ for 1 month induced microglial activation and inhibited LTP, with others showing that spatial learning was inhibited by infusion of $A\beta_{1\text{-}42}$ for 23 (Yamada *et al*., 1999), 20 or 80 days (Nakamura *et al*., 2001), $A\beta_{1\text{-}40}$ for 14 days (Nitta *et al*., 1997) or $A\beta_{1\text{-}40}$ + $A\beta_{1\text{-}42}$ for 1 or 2 months (Frautschy *et al*., 2001).

The Aβ-induced deficit in LTP in the dentate gyrus *in vivo* is associated with microglial activation and upregulation of inflammatory cytokines, with both the Aβ-induced microglial activation and decreased LTP being attenuated by IL-4, the polyunsaturated fatty acid, eicosapentaenoic acid and the HMG-CoA reductase inhibitor, atorvastatin (Clarke *et al*., 2007; Lynch *et al*., 2007; Lyons *et al*., 2007b; Minogue *et al*., 2007). Additionally, the Aβ-induced inhibitory effect on LTP in CA1 *in vitro* was attenuated by pretreatment of slices with CD200Fc, which potently decreased the associated microglial activation (Lyons *et al*., 2012).

3.2. Transgenic models of Alzheimer's disease and decreased LTP

There is no doubt that microglial activation and the accompanying neuroinflammatory changes are associated with neuronal deficits that characterize AD, but it is not known whether these changes drive the pathology and loss of neuronal function, or are a consequence of the pathological processes. Similarly, increased expression of markers of microglial activation is likely to be a unifying theme in the brain of all animal models of AD (Li *et al*., 2013). One might predict that animal models would provide a clear indication of whether or not microglial activation drives the Aβ accumulation or vice versa, however this has not been the case. A systematic examination of time-related changes in several parameters in 3 x Tg mice revealed that increased activation of microglia and astrocytes occurred at 2 months of age. This was accompanied by increased expression of human APP and limited co-staining of APP and Aβ, but it occurred in advance of any evidence of intracellular or extracellular staining of $A\beta_{1\text{-}42}$ (Mastrangelo and Bowers, 2008). The authors suggested that these findings are consistent with a role for microglial activation in Aβ deposition. In a separate study, it was suggested that microglial activation contributed to the neuronal loss in these animals (Janelsins *et al*., 2008). In contrast, albeit in a different model,

APP/PS1 mice, microglial ablation appeared to have no effect on amyloidosis (Grathwohl *et al*., 2009). In the same model, we found that mRNA expression of IL-1β, CD68 and CD11b, as well as the numbers of $CD11b^{+}CD80^{+}$ and $CD11b^{+}MHCII^{+}$ cells, were increased in brain tissue from 7-9 month-old APP/PS1 mice, and that this was accompanied by evidence of Aβ accumulation (Gallagher *et al*., 2013; O'Reilly and Lynch, 2012). In a separate study in 6 month-old APP/PS1 mice, we observed increases in concentrations of soluble and insoluble $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ but no increase in CD11b mRNA or in the number of $CD11b^{+}CD80^{+}$ or $CD11b^{+}CD86^{+}$ cells in the brain (McManus *et al*., 2014). These studies have not provided a clear indication that microglial activation contributes to deposition of Aβ, however several groups have reported that anti-inflammatory agents impact on Aβ accumulation, and also on the associated loss of synaptic plasticity (Li *et al*., 2013). A significant issue in the debate is the impact of an inflammatory microenvironment on phagocytic ability of microglia (and indeed macrophages). It has been reported that released inflammatory mediators and oxidative species from activated glia decrease phagocytic function (Hickman *et al*., 2008); others have similarly reported a negative impact of inflammatory mediators on microglial phagocytosis (Koenigsknecht and Landreth, 2004; Pan *et al*., 2011). In contrast anti-inflammatory cytokines, and microglia which adopt the M2 activation state, appear to facilitate phagocytosis (Hjorth *et al*., 2013; Koenigsknecht-Talboo and Landreth, 2005; Mandrekar-Colucci *et al*., 2012).

The accumulating Aβ burden, coupled with the associated microglial activation, appears to be irrevocably linked with a loss of synaptic plasticity in animals models of AD and, although it is not possible to identify the contribution of these factors separately, there is a great deal of evidence indicating that when the Aβ burden is reduced, synaptic plasticity is restored, at least to some extent as reviewed previously (Li *et al*., 2013; Marchetti and Marie, 2011). Among the first observations indicating that overexpression of APP, and the associated accumulation of Aβ, affected LTP was a study which reported that the deficit *in vivo* and *in vitro* was accompanied by an impairment in spatial working memory in 15−17 month-old APP_{695}SWE mice (Chapman *et al*., 1999). Since that time, similar deficits in LTP and spatial learning have been described in other transgenic mouse models, including mice which overexpress APP and presenilin 1 (APP/PS1 mice) and 3 x Tg mice which overexpress APP, PS1 and tau, as described in a number of comprehensive reviews (Braidy *et al*., 2012; Marchetti and Marie, 2011). While 6 month-old 3 x Tg mice exhibited a decrease in LTP in CA1, no change was observed in slices from 6 month-old APP/PS1 mice and it was suggested that the deficit was accounted for by an increase in intraneuronal Aβ (Oddo *et al*., 2003). There is not complete agreement regarding the time at which changes in plasticity become apparent since there are reports of decreased LTP in APP/PS1 mice at 6 months (Marchetti and Marie, 2011) and even as early as 3 months of age (Trinchese *et al*., 2004).

It is striking that many potential therapies have the ability to reduce Aβ accumulation and neuroinflammatory changes in animal models of AD, and at least some of these have been shown to attenuate the loss of plasticity; these factors include immune therapies, anti-oxidants and modulators of glutamatergic, cholinergic and adrenergic receptor signalling and are comprehensively described in a recent review (Li *et al*., 2013). Many impact on microglial function with evidence that acetylcholine and noradrenaline attenuate microglial activation (Carnevale *et al*., 2007), an effect that is also attributed to activation of metabotropic glutamate receptor subtype 5 (Loane *et al*., 2009). Interestingly, Aβ immunotherapy, in addition to decreasing the Aβ burden, is capable of switching microglia into an activated phagocytic state (Koenigsknecht-Talboo *et al*., 2008; Wilcock *et al*., 2003; Wilcock *et al*., 2004). Anti-inflammatory strategies which inhibit microglial activation have also been shown to be useful in attenuating some of the changes in models of AD, however

although there is some evidence that long-term use of non-steroidal antiinflammatory treatment may reduce the risk of AD, no beneficial effect in prospective clinical trials has been reported (Boche and Nicoll, 2008). There is, however, the caveat that if microglial activation is an event which triggers early changes, then treatment in established disease is unlikely to be especially advantageous.

Despite these promising pre-clinical leads, translation into clinical usefulness where deterioration of cognitive function is arrested or retarded, remains a challenge. Among the issues that need to be tackled is the ability of animal models to adequately reflect the full gamut of pathologies of AD and, in that context, identification of the triggers which precipitate the rapid loss of glial and neuronal function. Rational treatment strategies are likely to emanate from this, however the real key to successful treatment of AD is early diagnosis.

4. Conclusions

The negative impact of neuroinflammatory changes on neuronal function has been convincingly documented in the past decade or so and a key factor in driving neuroinflammation is glial activation, particularly activation of microglia. Although it is now accepted that microglia can adopt different activation states in response to diverse stimuli, in a manner somewhat analogous to macrophages, a great deal of work is necessary to gain a greater understanding of the functional phenotypes, the factors that control switching phenotypes *in situ* particularly in acute and chronic neuroinflammatory and/or neurodegenerative conditions, and the impact that switching might have on neuronal function.

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