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Invited review

Immune dysregulation and cognitive vulnerability in the aging brain: Interactions of microglia, IL-1β, BDNF and synaptic plasticity

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ABSTRACT

Older individuals often experience declines in cognitive function after events (e.g. infection, or injury) that trigger activation of the immune system. This occurs at least in part because aging sensitizes the response of microglia (the brain's resident immune cells) to signals triggered by an immune challenge. In the aging brain, microglia respond to these signals by producing more pro-inflammatory cytokines (e.g. interleukin-1beta or IL-1β) and producing them for longer than microglia in younger brains. This exaggerated inflammatory response can compromise processes critical for optimal cognitive functioning. Interleukin-1β is central to the inflammatory response and is a key mediator and modulator of an array of associated biological functions; thus its production and release is usually very tightly regulated. This review will focus on the impact of dysregulated production of IL-1β on hippocampus dependent-memory systems and associated synaptic plasticity processes. The neurotrophin brain-derived neurotrophic factor (BNDF) helps to protect neurons from damage caused by caused by infection or injury, and it plays a critical role in many of the same hippocampal plasticity and memory processes compromised by dysregulated production of IL-1β. This suggests that an exaggerated brain inflammatory response, arising from aging and a secondary immune challenge, may erode the capacity to provide the BDNF needed for memory-related plasticity processes at hippocampal synapses.

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1. Introduction

The range of cognitive functioning widens dramatically with aging. Some individuals reach advanced age with cognitive functions largely intact; many do not. Even previously high functioning aged individuals who experience an acute infection, injury or surgery are at increased risk for developing abrupt cognitive decline (sometimes termed delirium) – a rapidly developing, severe but often temporary memory impairment (Bekker and Weeks, 2003; Chan and Brennan, 1999; Fong et al., 2009; Pandharipande et al., 2005; Wofford et al., 1996). Even if these individuals recover from the delirium, they are at significantly greater risk of ultimately developing Alzheimer's disease or other forms of dementia (Chan and Brennan, 1999; Fong et al., 2009; Katz et al., 2001; McCusker et al., 2001). It is not clear if this increased risk occurs because the delirium represents the unmasking of existing, but early stage pathology, or if an episode of delirium is itself an insult that contributes to the development of lasting memory impairment. There is some evidence to support the late possibility since an infection, even in the absence of delirium, is associated with an increased risk of developing Alzheimer's disease (Dunn et al., 2005). In either case, the phenomena may provide a window into very early perturbations of systems critical for memory. It is very clear that a secondary immune challenge exacerbates cognitive decline in individuals already suffering from some degree of impairment, increasing the risk of developing delirium (or more gradual forms of cognitive decline) and worsening the prognosis (Cunningham et al., 2009; Perry et al., 2007; Perry and Holmes, 2014).

How then might an immune challenge compromise memory-related synaptic functions in aging brains?

2. The immune system in the periphery can communicate with the brain

A foundation for potential mechanisms is suggested by the fact that there is extensive communication between the peripheral

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immune system and the brain, and that this communication intensifies in response to an immune challenge (reviewed in (Dantzer et al., 2008; Konsman et al., 2002; Maier et al., 2001)). Pro-inflammatory cytokines like interleukin 1-alpha and beta (IL-1α and β), tumor necrosis factor-alpha (TNF-α), and interleukin 6 (IL-6) released in the periphery in response to infection or injury can communicate with the brain via humoral, and neural routes. These immune signaling routes (reviewed in (Dilger and Johnson, 2008; Nguyen et al., 2002; Quan and Banks, 2007; Wynne et al., 2009)) include (1) diffusion of circulating cytokines through areas adjacent to the circumventricular organs, which lack a contiguous blood–brain – the close proximity of these areas to the hypothalamus is thought to play a role in the cytokine driven "sickness behaviors" characterized by fever, anorexia, and malaise; (2) binding of circulating cytokines directly to receptors on the endothelial cells forming the blood–brain barrier, stimulating them to secrete cytokines and other immune molecules (e.g. NOS, etc.) directly into brain regions; (3) transport of peripheral cytokines by an energy-dependent, saturable process involving transporters integral in the blood–brain barrier; and (4) direct activation of vagal afferents and catecholaminergic circuits of the sympathetic nervous system by circulating cytokines. These immune signals from the periphery can be detected by microglia, the brain's primary resident immune cells (reviewed in (Dantzer et al., 2008; Konsman et al., 2002; Maier et al., 2001). Microglia can respond to these stimuli –propagating immune signals from the periphery – by producing additional pro-inflammatory cytokines (e.g. TNFα, IL-6, IL-1β, interferon-γ (IFNγ)) and several chemokines in the CNS (reviewed in (Cherry et al., 2014)).

In addition to cytokine and chemokine receptors, microglia have a vast array of receptors capable of detecting additional evidence of infection or injury. The receptors recognize the small molecular motifs or patterns found on pathogens, or associated with tissue damage. These pattern recognition receptors (PRRs) include toll-like receptors (TLRs), nucleotide-binding oligomerization domains (NODs), NOD-like receptors (NLRs), and a number of scavenger receptors (Canton et al., 2013; Cherry et al., 2014; Ransohoff and Brown, 2012; Ransohoff and Perry, 2009).

3. Microglia serve many functions in the brain

The last decade has seen a major expansion in our understanding of the roles played by microglia in the brain (reviewed in (Hughes, 2012; Raivich, 2005; Streit and Xue, 2009; Yirmiya and Goshen, 2011)).

It has long been recognized that microglia are activated in response to insult and disease, and that they play a central role in pathophysiology. More recently, it has become apparent that the process of microglial activation is gradual, very complex, and highly varied. There can be multiple activation sub-states, with associated changes in structure (e.g. retraction and reduction of elaborate thin processes to transform into a more ameboid form), and function (e.g. altered expression of various receptors and enzymes; and production of immune response molecules and growth factors). Although incompletely understood, the assumption of different immune phenotypes by microglia seems to depend on some combination prior history and current microenvironment (reviewed in (Cherry et al., 2014; Goldmann and Prinz, 2013; Mittelbronn, 2014; Perry, 2004)).

This situation is often compared to the multiple and sometimes opposing activation states (and associated functions) of peripheral macrophages – termed classical and alternative, or M1 and M2 activation (paralleling the Th1 terminology used for T cells) (reviewed in (Cherry et al., 2014; Goldmann and Prinz, 2013; Mittelbronn, 2014; Perry, 2004)). Although some caution is indicated in extrapolating from peripheral to CNS and in vitro to in vivo systems, this seems a useful, if still somewhat controversial organizational distinction. In very general terms, the initial, classically activated, M1 state is associated with mounting a defense against infection and is considered pro-inflammatory. The alternatively activated, M2 state is generally, though perhaps not always, less inflammatory and associated more with suppressing inflammation, conducting repairs and restoring homeostasis (reviewed in (Cherry et al., 2014; Goldmann and Prinz, 2013; Mittelbronn, 2014; Perry, 2004)).

Thus, depending on the nature, severity and duration of the immune challenge, microglia can take on a number of phenotypes, orchestrate a variety of inflammatory responses, perform cleanup of dead cells and debris, and assist with regeneration (reviewed in (Kreutzberg, 1996; Prinz and Priller, 2014; Streit and Xue, 2009; Wong, 2013)). Microglia also play an active role in removing damaged or dysfunctional synapses – a process termed synaptic stripping (Blinzinger and Kreutzberg, 1968; Kettenmann et al., 2013). However, microglia have traditionally been thought to be relatively quiescent in a normal health brain (Morris et al., 2013). It is now recognized that "resting" microglia are actually quite active – dynamically surveying their environment (Davalos et al., 2005; Nimmerjahn et al., 2005), pruning inappropriate or underperforming synapses and refining synaptic circuits during development (and possibly into adulthood) (Paolicelli et al., 2011; Schafer et al., 2012; Tremblay et al., 2010), and helping to support neuronal survival and function (Streit et al., 2009). In addition to the canonical cytokines (e.g. IL-1β, IL-6 and TNF-α), both resting and activated microglial can produce a range of soluble factors also capable of modulating synaptic function (reviewed in (Morris et al., 2013; Streit and Xue, 2012; Wong, 2013)). These include trophic factors (e.g. BDNF (Batchelor et al., 1999; Elkabes et al., 1996; Nakajima et al., 2002; Suzuki et al., 2001) and NGF (Frade and Barde, 1998; Mallat et al., 1989)), neurotransmitters, and neuromodulators.

4. Microglial functioning changes with aging

Microglia undergo significant changes in the aging brain. They tend to have a more irregular distribution, with shorter, less elaborated processes (reviewed in (Wong, 2013)). Although the consequences of these changes are not well understood, they may reflect a decline, or perhaps a more nuanced dysregulation in the protective and or supportive capacity of individual microglial cells. Interestingly, even in the absence of injury or disease, the basal activation state of microglial in aging (but not yet senescent) brains appears to be higher (Frank et al., 2006; Perry et al., 1993; Rogers et al., 1988). Microglia in aging brains show increased expression of several inflammatory markers including molecules involved in presentation of antigens (major histocompatibility complex II (MHC II) and CD86), and membrane pattern associated recognition receptors (Toll-like receptors (TLRs)). There are also indications of aging-associated alterations (for a recent review see (Lynch, 2014)) in cytosolic pattern receptors (NOD-like receptors (NLRs); e.g. NLRP1 & NLRP3) that form part of the inflammasome complex involved in activation of caspase-1, and the subsequent cleavage and release of IL-1β and IL-18 – another member of the IL-1 family (Rathinam et al., 2012; Walsh et al., 2014).

These alterations are consistent with an aging-associated sensitization or "priming" of microglia (Norden and Godbout, 2013), and indeed, microglial responsiveness to signals from the peripheral immune system and the local environment is exaggerated. In addition to increasing the potential for transition into full, prolonged and potentially harmful inflammation (reviewed in (Medzhitov, 2008; Wong, 2013)), the sensitization of microglia in

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the aging brain may also lead to disruption of many of their normal physiological roles, including modulation of synaptic structure and function.

A consistent finding in rodent models has been that, in response to a peripheral immune challenge, the brains of aging animals produce significantly more pro-inflammatory cytokines (e.g. IL-1β, IL-6 and TNF-α), and produce them longer than those of younger cohorts (Barrientos et al., 2006; Chen et al., 2008; Godbout et al., 2005) (reviewed in (Dilger and Johnson, 2008)). For example, when aged mice received an intraperitoneal (i.p.) injection of bacterial cell wall lipopolysaccharide (LPS) (Drum and Oppemtom, 1989) – at a dose that induces a mild transient sickness behavior in young adults (Berg et al., 2004) – the LPS-evoked increase in IL-1β was significantly larger than in young mice (Godbout et al., 2005). Another study found that after i.p. LPS, aged mice had more microglial cells in the hippocampus, and more IL-1β-positive cells in hippocampal areas CA1, CA2, and CA3 and dentate than young controls (Chen et al., 2008). Similarly, aging rats showed higher hippocampal IL-1β protein levels than their younger counterparts a few hours after an i.p. injection of *Escherichia coli*, and the duration of these elevations was significantly longer than that in younger controls (Barrientos et al., 2009).

5. The hippocampus is a major site of expression of IL-1β and its receptor in the brain

Interleukin1β, its receptor, and the naturally occurring interleukin-1 receptor antagonist (IL-1ra) (Lechan et al., 1990) (Ban et al., 1991; Takao et al., 1990) are all found at comparatively high levels in the hippocampus – a brain structure known to be critical for spatial and contextual memory (Smith and Mizumori, 2006; Squire et al., 2004). This expression pattern suggests that these molecules have the potential to modulate hippocampal memory functions, and supports the hypothesis that excessive (or perhaps otherwise dysregulated) IL-1 signaling might contribute to deficits in hippocampus-dependent memory processes.

6. Aberrantly elevated levels of IL-1β may impair memory

Numerous studies have provided evidence that experimentally elevated levels of IL-1β in the hippocampus can impair performance in behavioral paradigms (e.g. the Morris water maze (Morris, 1984) and contextual fear conditioning (Kim and Fanselow, 1992; Phillips and LeDoux, 1992)) commonly used to examine hippocampus-dependent memory (reviewed in (Lynch, 2010; Yirmiya and Goshen, 2011)). The deleterious effect of IL-1β on consolidation of spatial memory was first demonstrated by injecting IL-1β into the ventricles of rats and accessing their performance in Morris maze. The IL-1β did not affect the acquisition of the spatial navigational task, but rather its retention (Oitzl et al., 1993). Subsequent experiments in rodents have confirmed and extended this observation, demonstrating similar, specific impairments in hippocampus-dependent contextual tasks following intraperitonneal (Gibertini et al., 1995) or intrahippocampal injection of IL-1β (Barrientos et al., 2002), prolonged (2 week) elevation of IL-1β in an inducible transgenic mouse (Hein et al., 2010), and elevations in endogenous IL-1β evoked by infections (Barrientos et al., 2006; Chen et al., 2008; Gibertini et al., 1995) or psychological stressors (Pugh et al., 1999).

Multiple observations provide evidence that excess brain IL-1β may play a pivotal role in these impairments. Levels of hippocampal IL-1β and the deficits in hippocampus-dependent memory are tightly, and inversely correlated over time (Barrientos et al., 2009; Goshen et al., 2007). The deficits can be blocked by intraventricular infusion of the naturally occurring interleukin-1 receptor antagonist (IL-1ra) (Dinarello, 1997) concurrent with the peripheral immune challenge (Frank et al., 2010).

However, it should noted that while excess hippocampal IL-1β has a deleterious effect on memory, low levels of IL-1β appear to be required for consolidation of context-dependent memory (reviewed in (Yirmiya and Goshen, 2011)). In a health brain, in the absence of injury or infection, levels of IL-1β are generally low, but they are upregulated by contextual fear learning (Goshen et al., 2007), and spontaneous spatial recognition in the Y-maze paradigm (Labrousse et al., 2009). Conversely, contextual memory is impaired by genetic reduction of endogenous IL-1β signaling (Azouz et al., 1996; Goshen et al., 2007). A recent study utilizing systematic intra-ventricular infusion of different doses of IL-1β and IL-1ra into mice has provided compelling pharmacological evidence that the effects of hippocampal IL-1β on memory follow a U-shaped dose–response curve (Goshen et al., 2007). Slight, transient elevations in IL-1β improved memory, but levels in excess of or below the physiological range resulted in deficits in hippocampus-dependent memory (Goshen et al., 2007).

7. IL-1β can modulate synaptic plasticity

Hippocampal long-term potentiation (LTP) is generally considered to be a substrate for hippocampus-dependent memory, so it is not surprising that memory deficits driven by excessive IL-1β are paralleled by deficits in LTP. Experimentally elevated levels of IL-1β have been shown to inhibit LTP in several regions of the hippocampus in young animals (reviewed in (Lynch, 2010)). Application of IL-1β to rodent hippocampal slices reduced LTP in CA1 (Bellinger et al., 1993; Ross et al., 2003), while heat-inactivated IL-1β had no effect (Bellinger et al., 1993). Treatment of mouse slices with high levels (in the pathophysiological range) of IL-1β resulted in a similar reduction in area CA1 LTP, but this was also true of treatment with a high dose of IL-1ra (Ross et al., 2003). Application of exogenous IL-1β inhibited LTP in the CA3 region of mouse hippocampal slices (Katsuki et al., 1990), and the dentate in rat hippocampal slices (Coogan and O'Connor, 1997; Cunningham et al., 1996). These effects of the IL-1β could be blocked by concurrent application of an inactive analog of IL-1β or IL-1ra (Coogan and O'Connor, 1997; Cunningham et al., 1996; Katsuki et al., 1990). Injecting IL-1β directly into the ventricles inhibited LTP in the dentate in vivo (Kelly et al., 2003; Murray and Lynch, 1998), as did an i.p. injection of LPS (Barry et al., 2005; Lynch et al., 2004).

Using *E. coli* as the peripheral immune stimulus in aged, but cognitively intact rats, evoked an exaggerated (relative to younger counterparts) elevation in hippocampal IL-1β, mirrored by specific deficits in consolidation of context-dependent learning (Barrientos et al., 2006). Task acquisition and short-term memory were preserved. Interestingly, the deficits in synaptic plasticity in these animals appeared to be similarly specific. Basal synaptic transmission and short-term synaptic plasticity remained intact in area CA1 of hippocampal slices from the aging rats after infection. However, these animals had profound deficits in a form of long-lasting synaptic plasticity (late-phase LTP or L-LTP) (Chapman et al., 2010), evoked by a relatively naturalistic stimulus (theta burst), and strongly correlated with the ability to consolidate contextual memory in aged rats (Tombaugh et al., 2002). Importantly, like the deficits in consolidation, the deficits in theta burst L-LTP could be blocked with IL-1ra (Chapman et al., 2010). However, IL-1ra also blocks the effects of IL-18, another member of the IL-1 family, also shown to attenuate LTP in the dentate gyrus (Curran and O'Connor, 2001), so the blockade of infection-induced deficits may not be exclusively attributable to blocking the effects of IL-1β.

Just as low (physiological) levels of IL-1β appear to be necessary for consolidation of contextual memory, they also appear to be

required for long-lasting LTP. Expression of IL-1β is induced by stimuli producing LTP both in vivo and in slices (Schneider et al., 1998). Early LTP evoked by a single train of high frequency stimulation is reported to be normal in slices from IL-1 α/β double knockout mice (Ikegaya et al., 2003), but L-LTP is impaired in slices from IL-1 receptor type I knockout (IL-1rKO) mice (Avital et al., 2003), and slices from wild-type mice treated with IL-1ra (Ross et al., 2003).

8. Potential mechanisms

It is not clear how aberrantly elevated levels of IL-1β in the hippocampus may produce impairments in synaptic plasticity and memory. Available data suggest multiple, sometimes converging mechanisms.

A number of recent studies have provided evidence that pro-inflammatory cytokines can modulate responses to glutamate through complex effects on NMDA and AMPA receptor function (reviewed in (Viviani and Boraso, 2011)). Acute application of IL-1β has generally been shown to reduce Area CA1 plasticity in hippocampal slices and in vivo (Bellinger et al., 1993; Lynch, 2010; Ross et al., 2003). However, Nistico and colleagues (Nistico et al., 2013) have reported that acute application of IL-1β increased early LTP (evoked by a single train of high frequency stimulation) in hippocampal slices from mice previously injected with complete Freund's adjuvant (CFA) (an inflammatory agent sometimes used as an immunobooster for other autoantigens). Effects on NMDA receptor-mediated currents show similar variability, with both reductions and enhancements (and accompanying stabilization of the NMDA receptor in the synapse) reported (Coogan and O'Connor, 1997; Viviani et al., 2003).

Chronic elevations in IL-1β also produce varied effects on synaptic plasticity. Intraventricular infusions of LPS over 28 days have been reported to produce reductions in NMDAR-dependent and NMDAR-independent forms of LTP evoked by high frequency and theta burst stimulation (Min et al., 2009). Effects of a more limited, one time immune challenge with *E. coli* appear to be more specific – reducing theta burst evoked L-LTP, while leaving E-LTP and high frequency train-evoked L-LTP intact (Chapman et al., 2010). In contrast, when E-LTP was examined in hippocampal slices from mice with experimental autoimmune encephalomyelitis (EAE) – a mouse model of multiple sclerosis (MS) – it was enhanced relative to that in CFA controls (injected with CFA without the EAE-inducing autoantigen) (Nistico et al., 2013). When IL-1β was acutely applied to the slices from the CFA controls, the E-LTP was comparable to that in slices from the EAE mice. Increased glutamate transmission (and associated excitotoxicity) is thought to play a role in the inflammation-driven neurodegenerative process of MS. In the model system used by Nistico et al., IL-1β secreted by activated microglia was found to suppress GABAergic inhibitory transmission, with limited effects on glutaminergic transmission – in contrast to the impaired hippocampal glutamatergic transmission observed in another EAE model (Xing et al., 2011). However, in both cases the normal balance between excitation and inhibitory inhibition was disrupted, subverting normal synaptic function.

Other potential mechanisms for the effects of IL-1 on plasticity and memory may involve activation of p38 mitogen-activated protein kinase (MAPK), c-jun NH_2-terminal kinase (JNK), caspase 1, and NFkB (Curran et al., 2003; Kelly et al., 2003; Tong et al., 2012; Vereker et al., 2000a, 2000b). These molecules lie within, and in some cases link, multiple signaling cascades likely to play a role in inflammation-driven cognitive impairments (Tong et al., 2012). Intriguingly, these cascades also intersect with those sometimes used by the neurotrophin BDNF. BDNF plays a critical role in the survival and development of certain populations of neurons. BDNF can also be neuroprotective, mitigating the damaging effects of a variety of insults. In addition, BDNF plays a central role in forms of long-lasting synaptic plasticity associated with consolidation of hippocampus-dependent memory (Bramham and Messaoudi, 2005; Lu, 2003; Tyler et al., 2002) – the same memory-related plasticity processes compromised by excessive IL-1β.

The capacity to produce BDNF is generally very tightly controlled. The gene gives rise to numerous BDNF mRNA transcripts, all of which are translated into the same protein. All of the transcripts are found in the hippocampus, though at different levels, and with different cellular and subcellular distributions (An et al., 2008; Kokaia et al., 1994; Timmusk et al., 1993). Their expression is differentially regulated by a variety of inputs including alterations in neuronal activity (Metsis et al., 1993; Nakayama et al., 1994; Timmusk et al., 1993), exercise (e.g. (Garcia et al., 2003; Oliff et al., 1998)), treatment with antidepressants (Russo-Neustadt et al., 2004), and various stress paradigms (reviewed in (Lauterborn et al., 1998)).

Infusion of IL-1β into the hippocampus decreased its capacity for transcription of BDNF following learning (Barrientos et al., 2004), and infusion of IL-1ra protected it from the deleterious effects of IL-1β induced by a social isolation stress paradigm (Barrientos et al., 2003). Since slight, transient elevations in IL-1β improved hippocampus-dependent memory, but levels in excess of or below the physiological range resulted in deficits (Goshen et al., 2007), it seemed plausible that a similar relationship might be observed with the expression of BDNF. It has recently been reported that a single intracerebroventricular (i.c.v.) injection of IL-1β increased expression of BDNF mRNA, but 8 days of repeated injections did the opposite (Song et al., 2013). However, this is in contrast to the results of an earlier study that found that a single injection of LPS resulted in deficits in spatial learning, while repeated injections apparently did not (though these rats showed evidence of significant sickness behavior), and neither treatment produced any alteration in BDNF mRNA in the dentate at the time point examined (Shaw et al., 2001).

As the authors of Shaw et al. note, the links between alterations in IL-1 and BDNF expression are likely to be highly dependent on subject, manipulation, assay and timing of assay. Highlighting these potential subtleties, aging and a recent *E. coli* infection in rats reduced the hippocampal expression of specific activity-and plasticity-associated BDNF mRNA transcripts, and reduced the capacity to recruit these transcripts following learning (Chapman et al., 2012).

The BDNF protein is synthesized as a precursor proBDNF molecule that is cleaved to produce mature BDNF (mBDNF). Interestingly, the pro- and mature forms of BDNF can activate different receptors, intracellular pathways, and cellular functions and they have generally opposing effects (Lu et al., 2005). Pro-BDNF binds preferentially to the pan-neurotrophin receptor $p75^{NTR}$ (a member of the tumor necrosis factor receptor superfamily), elicits neuronal apoptosis (Friedman, 2010; Lee et al., 2001; Teng et al., 2005; Volosin et al., 2006), and facilitates long-term depression (LTD) in the hippocampus (Rosch et al., 2005; Woo et al., 2005). In contrast, mature BDNF binds to the TrkB receptor, promotes cell survival (Volosin et al., 2006), and facilitates LTP. Activation of $p75^{NTR}$ reduces dendritic complexity and spine density in the hippocampus; activation of TrkB does the opposite (McAllister et al., 1999; Zagrebelsky et al., 2005). There was initially considerable controversy about whether proBDNF was secreted in non-pathological conditions (Matsumoto et al., 2008; Yang et al., 2009) (reviewed in (Barker, 2009)), but recent studies support a role in normal developmental programmed cell death and pruning of dysfunctional or rejected connections (Je et al., 2012; Taylor et al., 2012) reviewed in (Deinhardt and Chao, 2014).

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Interestingly, the combination of aging and an *E. coli* immune challenge was associated with reduced levels of the mature BDNF protein isoform in hippocampal synaptoneurosomes (Cortese et al., 2011). The reduction could be blocked with IL-1ra. Levels of the pan-neurotrophin receptor p75NTR and the BDNF receptor TrkB were not significantly altered. However, activation of TrkB, and downstream activation of PLCγ1 (phospholipase Cγ1) and p40/42 MAPK, but apparently not PI3-K/Akt was attenuated. These observations are consistent with reduced availability of mature BDNF to activate TrkB signaling for memory-related plasticity processes.

There are also indications that IL-1β can compromise neuronal survival by interfering with the neuroprotective effect of BDNF. Using primary cultures of trophic support-deprived cortical neurons, Tong and colleagues found that IL-1β didn't affect the activation of TrkB receptors, but instead altered BDNF signaling at the level of the docking sites for proteins mediating the signaling functions of the receptor (Tong et al., 2008). IL-1β did not alter the activation of PLC gamma, but suppressed activation the docking proteins linked to activation of the p40/42 MAPK and survival promoting PI3-K/Akt pathways. This effect of IL-1β appeared to involve the activation of the ceramide pathway, since the IL-1β induced suppression of BDNF neuro-protection and signal transduction could be reduced by inhibitors of ceramide production, and mimicked by the cell-permeable C2 ceramide (Tong et al., 2008). Activation of the ceramide pathway is known to increase with aging and many neurodegenerative diseases (Cutler et al., 2004).

Tong et al. also found additional evidence consistent with the idea that excessive production of IL-1β might disrupt BDNF-dependent synaptic plasticity processes (Tong et al., 2012). Addition of IL-1β to organotypic rat hippocampal cultures suppressed BDNF-dependent regulation of Arc and cAMP response element-binding protein (CREB). IL-1β upregulated p38 mitogen-activated protein kinase (MAPK), and inhibiting p38 MAPK prevented IL-1β from disrupting BDNF signaling. In acute hippocampal slices, IL-1β blocked the formation of filamentous actin (F-actin) in dendritic spines (required for the production of L-LTP) and disrupted the consolidation, but not the induction, of theta-burst induced BDNF-dependent LTP. Inhibiting p38 MAPK also blocked these effects of IL-1β (Tong et al., 2012).

These results are particularly interesting in light of recent studies demonstrating a rich and varied role for microglia in shaping appropriate synaptic connectivity during development and into adulthood (Paolicelli et al., 2011; Parkhurst et al., 2013; Zhan et al., 2014) — functions frequently mediated by BDNF. Neurons are the major source of BDNF in the healthy adult brain (Rauskolb et al., 2010), but a recent study suggests that BDNF from microglial can also contribute to learning-related synapse formation (Parkhurst et al., 2013). Conditional removal of BDNF from microglia resulted in deficits in motor-learning tasks and in learning-dependent synapse formation. These deficits were very similar to those seen in mice with targeted, diphtheria toxin-driven depletion of microglia (Parkhurst et al., 2013). Together, these observations suggest that aging-associated, inflammation-driven alterations in microglia BDNF might also contribute to cognitive deficits.

Data from conventional aging and neurodegenerative disease models suggest that when age-related cognitive deficits occur, they do not arise from loss of neurons, or initially even from loss of synapses (Geinisman et al., 2004; Rapp and Gallagher, 1996), but rather from more subtle alterations in synaptic efficacy (Rapp et al., 1999; Selkoe, 2002; Smith et al., 2000). BDNF is a key mediatory of synaptic efficiency. BDNF regulates dendritic (local) protein synthesis (Aakalu et al., 2001), thought to be a mechanism by which the protein complement of individual synapses can be altered and long-lasting changes in efficiency can be maintained (Schuman et al., 2006). BDNF can also regulate the structural plasticity of individual dendrites spines (Tanaka et al., 2008), an observation that has led observers to suggest a link between aging-associated alterations in dendritic spines and reduced expression of BDNF and TrkB (Tapia-Arancibia et al., 2008).

It's long been suspected that disruptions in BDNF production, processing or signaling might be a significant factor in the development and or progression of age-associated cognitive decline. Rather surprisingly, the available evidence suggests that basal levels of BDNF and its receptor TrkB do not change greatly as a result of aging alone (reviewed in (Pang and Lu, 2004)), although BDNF is significantly reduced in Alzheimer's disease (Phillips et al., 1991). The observation that aging increases cognitive vulnerability to infection suggests a new twist on an old theme. Perhaps is not aging *per se* that disrupts BDNF-dependent processes in the hippocampus, but rather the combination of aging and challenging life events.

9. Concluding remarks

Aging increases cognitive vulnerability to secondary stressors, particularly those that produce a significant peripheral immune response. Although relatively little is known about the underlying mechanisms, the data available suggest that immune signals from the periphery trigger an exaggerated inflammatory response in the aging brain, which in turn compromises plasticity processes required for cognitive functions.

Aging-associated dysregulation of microglial function appears to be a critical component of this progression. Microglia can take on a variety of phenotypes and perform a wide range of important functions: surveillance for indications of infection or injury, orchestration of inflammatory processes, clearance of dead cells and debris, stripping of damaged synapses, promoting a return to homeostasis, and as recently recognized, helping to establish and maintain appropriate neuronal connectivity. Aging induces a shift in microglial phenotype, sensitizing them to immune stimuli, which can further tip the balance between pro-inflammatory (M1) and more anti-inflammatory (M2) phenotypes. Similar mechanisms may contribute to increased risk of cognitive dysfunction in a variety of disorders associated with some degree of potentially "sensitizing" inflammation (e.g. autoimmune diseases, depression, diabetes, and head injury (Perry et al., 2007)).

In the aging brain, immune challenge-evoked overproduction of IL-1β by microglia has been shown to produce specific deficits in consolidation of hippocampus-dependent memory, and associated forms of synaptic-plasticity. These are BDNF-dependent processes, and excess IL-1β appears to disrupt BDNF production and signaling. Inflammation-driven alterations in BDNF signaling may be one mechanism by which microglial dysregulation can produce discrete, but deleterious alterations in synaptic structure and function. However, there are undoubtedly others.

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References

Aakalu, G., Smith, W.B., Nguyen, N., Jiang, C., Schuman, E.M., 2001. Dynamic visualization of local protein synthesis in hippocampal neurons. Neuron 30, 489–502.

An, J.J., Gharami, K., Liao, G.Y., Woo, N.H., Lau, A.G., Vanevski, F., Torre, E.R., Jones, K.R., Feng, Y., Lu, B., Xu, B., 2008. Distinct role of long 3' UTR BDNF mRNA

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in spine morphology and synaptic plasticity in hippocampal neurons. Cell 134, 175–187.
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, 826–834.
Azouz, R., Jensen, M.S., Yaari, Y., 1996. Ionic basis of spike after-depolarization and burst generation in adult rat hippocampal CA1 pyramidal cells. J. Physiol. 492 (Pt 1), 211–223.
Ban, E., Milon, G., Prudhomme, N., Fillion, G., Haour, F., 1991. Receptors for interleukin-1 (alpha and beta) in mouse brain: mapping and neuronal localization in hippocampus. Neuroscience 43, 21–30.
Barker, P.A., 2009. Whither proBDNF? Nat. Neurosci. 12, 105–106.
Barrientos, R.M., Frank, M.G., Hein, A.M., Higgins, E.A., Watkins, L.R., Rudy, J.W., Maier, S.F., 2009. Time course of hippocampal IL-1 beta and memory consolidation impairments in aging rats following peripheral infection. Brain Behav. Immun. 23, 46–54.
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, 723–732.
Barrientos, R.M., Higgins, E.A., Sprunger, D.B., Watkins, L.R., Rudy, J.W., Maier, S.F., 2002. Memory for context is impaired by a post context exposure injection of interleukin-1 beta into dorsal hippocampus. Behav. Brain Res. 134, 291–298.
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, 221–231.
Batchelor, P.E., Liberatore, G.T., Wong, J.Y., Porritt, M.J., Frerichs, F., Donnan, G.A., Howells, D.W., 1999. Activated macrophages and microglia induce dopaminergic sprouting in the injured striatum and express brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor. J. Neurosci. 19, 1708–1716.
Bekker, A.Y., Weeks, E.J., 2003. Cognitive function after anaesthesia in the elderly. Best. Pract. Res. Clin. Anaesthesiol. 17, 259–272.
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, 227–234.
Berg, B.M., Godbout, J.P., Kelley, K.W., Johnson, R.W., 2004. Alpha-tocopherol attenuates lipopolysaccharide-induced sickness behavior in mice. Brain Behav. Immun. 18, 149–157.
Blinzinger, K., Kreutzberg, G., 1968. Displacement of synaptic terminals from regenerating motoneurons by microglial cells. Z Zellforsch. Mikrosk. Anat. 85, 145–157.
Bramham, C.R., Messaoudi, E., 2005. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. Prog. Neurobiol. 76, 99–125.
Canton, J., Neculai, D., Grinstein, S., 2013. Scavenger receptors in homeostasis and immunity. Nat. Rev. Immunol. 13, 621–634.
Chan, D., Brennan, N.J., 1999. Delirium: making the diagnosis, improving the prognosis. Geriatrics 54, 28–30, 36, 39–42.
Chapman, T.R., Barrientos, R.M., Ahrendsen, J.T., Hoover, J.M., Maier, S.F., Patterson, S.L., 2012. Aging and infection reduce expression of specific brain-derived neurotrophic factor mRNAs in hippocampus. Neurobiol. Aging 33, 832 e831–832 e814.
Chapman, T.R., Barrientos, R.M., Ahrendsen, J.T., Maier, S.F., Patterson, S.L., 2010. Synaptic correlates of increased cognitive vulnerability with aging: peripheral immune challenge and aging interact to disrupt theta-burst late-phase long-term potentiation in hippocampal area CA1. J. Neurosci. 30, 7598–7603.
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, 301–311.
Cherry, J.D., Olschowka, J.A., O'Banion, M.K., 2014. Neuroinflammation and M2 microglia: the good, the bad, and the inflamed. J. Neuroinflamm. 11, 98.
Coogan, A., O'Connor, J.J., 1997. Inhibition of NMDA receptor-mediated synaptic transmission in the rat dentate gyrus in vitro by IL-1 beta. Neuroreport 8, 2107–2110.
Cortese, G.P., Barrientos, R.M., Maier, S.F., Patterson, S.L., 2011. Aging and a peripheral immune challenge interact to reduce mature brain-derived neurotrophic factor and activation of TrkB, PLCgamma1, and ERK in hippocampal synaptoneurosomes. J. Neurosci. 31, 4274–4279.
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.
Cunningham, C., Campion, S., Lunnon, K., Murray, C.L., Woods, J.F., Deacon, R.M., Rawlins, J.N., Perry, V.H., 2009. Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. Biol. Psychiatry 65, 304–312.
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, 347–357.
Cutler, R.G., Kelly, J., Storie, K., Pedersen, W.A., Tammara, A., Hatanpaa, K., Troncoso, J.C., Mattson, M.P., 2004. Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 101, 2070–2075.
Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–56.
Davalos, D., Grutzendler, J., Yang, G., Kim, J.V., Zuo, Y., Jung, S., Littman, D.R., Dustin, M.L., Gan, W.B., 2005. ATP mediates rapid microglial response to local brain injury in vivo. Nat. Neurosci. 8, 752–758.
Deinhardt, K., Chao, M.V., 2014. Shaping neurons: long and short range effects of mature and proBDNF signalling upon neuronal structure. Neuropharmacology 76 (Pt C), 603–609.
Dilger, R.N., Johnson, R.W., 2008. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. J. Leukoc. Biol. 84, 932–939.
Dinarello, C.A., 1997. Interleukin-1. Cytokine Growth Factor Rev. 8, 253–265.
Drum, S.K., Oppemtom, J.J., 1989. Macrophage derived mediators: IL1, TNF, IL6, IGN and related signals. In: F, P.W. (Ed.), Fundemental Immunology. Raven, New York, pp. 639–661.
Dunn, N., Mullee, M., Perry, V.H., Holmes, C., 2005. Association between dementia and infectious disease: evidence from a case-control study. Alzheimer Dis. Assoc. Disord. 19, 91–94.
Elkabes, S., DiCicco-Bloom, E.M., Black, I.B., 1996. Brain microglia/macrophages express neurotrophins that selectively regulate microglial proliferation and function. J. Neurosci. 16, 2508–2521.
Fong, T.G., Tulebaev, S.R., Inouye, S.K., 2009. Delirium in elderly adults: diagnosis, prevention and treatment. Nat. Rev. Neurol. 5, 210–220.
Frade, J.M., Barde, Y.A., 1998. Microglia-derived nerve growth factor causes cell death in the developing retina. Neuron 20, 35–41.
Frank, M.G., Barrientos, R.M., Biedenkapp, J.C., Rudy, J.W., Watkins, L.R., Maier, S.F., 2006. mRNA up-regulation of MHC II and pivotal pro-inflammatory genes in normal brain aging. Neurobiol. Aging 27, 717–722.
Frank, M.G., Barrientos, R.M., Hein, A.M., Biedenkapp, J.C., Watkins, L.R., Maier, S.F., 2010. IL-1RA blocks E. coli-induced suppression of Arc and long-term memory in aged F344xBN F1 rats. Brain Behav. Immun. 24, 254–262.
Friedman, W.J., 2010. Proneurotrophins, seizures, and neuronal apoptosis. Neuroscientist 16, 244–252.
Garcia, C., Chen, M.J., Garza, A.A., Cotman, C.W., Russo-Neustadt, A., 2003. The influence of specific noradrenergic and serotonergic lesions on the expression of hippocampal brain-derived neurotrophic factor transcripts following voluntary physical activity. Neuroscience 119, 721–732.
Geinisman, Y., Ganeshina, O., Yoshida, R., Berry, R.W., Disterhoft, J.F., Gallagher, M., 2004. Aging, spatial learning, and total synapse number in the rat CA1 stratum radiatum. Neurobiol. Aging 25, 407–416.
Gibertini, M., Newton, C., Friedman, H., Klein, T.W., 1995. Spatial learning impairment in mice infected with Legionella pneumophila or administered exogenous interleukin-1-beta. Brain Behav. Immun. 9, 113–128.
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, 1329–1331.
Goldmann, T., Prinz, M., 2013. Role of microglia in CNS autoimmunity. Clin. Dev. Immunol. 2013, 208093.
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, 1106–1115.
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, 243–253.
Hughes, V., 2012. Microglia: the constant gardeners. Nature 485, 570–572.
Ikegaya, Y., Delcroix, I., Iwakura, Y., Matsuki, N., Nishiyama, N., 2003. Interleukin-1beta abrogates long-term depression of hippocampal CA1 synaptic transmission. Synapse 47, 54–57.
Je, H.S., Yang, F., Ji, Y., Nagappan, G., Hempstead, B.L., Lu, B., 2012. Role of pro-brain-derived neurotrophic factor (proBDNF) to mature BDNF conversion in activity-dependent competition at developing neuromuscular synapses. Proc. Natl. Acad. Sci. U. S. A. 109, 15924–15929.
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, 323–326.
Katz, I.R., Curyto, K.J., TenHave, T., Mossey, J., Sands, L., Kallan, M.J., 2001. Validating the diagnosis of delirium and evaluating its association with deterioration over a one-year period. Am. J. Geriatr. Psychiatry 9, 148–159.
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, 19453–19462.
Kettenmann, H., Kirchhoff, F., Verkhratsky, A., 2013. Microglia: new roles for the synaptic stripper. Neuron 77, 10–18.
Kim, J.J., Fanselow, M.S., 1992. Modality-specific retrograde amnesia of fear. Science 256, 675–677.
Kokaia, Z., Metsis, M., Kokaia, M., Bengzon, J., Elmer, E., Smith, M.L., Timmusk, T., Siesjo, B.K., Persson, H., Lindvall, O., 1994. Brain insults in rats induce increased expression of the BDNF gene through differential use of multiple promoters. Eur. J. Neurosci. 6, 587–596.

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Konsman, J.P., Parnet, P., Dantzer, R., 2002. Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci. 25, 154–159.
Kreutzberg, G.W., 1996. Microglia: a sensor for pathological events in the CNS. Trends Neurosci. 19, 312–318.
Labrousse, V.F., Costes, L., Aubert, A., Darnaudery, M., Ferreira, G., Amedee, T., Laye, S., 2009. Impaired interleukin-1beta and c-Fos expression in the hippocampus is associated with a spatial memory deficit in P2X(7) receptor-deficient mice. PLoS One 4, e6006.
Lauterborn, J.C., Poulsen, F.R., Stinis, C.T., Isackson, P.J., Gall, C.M., 1998. Transcript-specific effects of adrenalectomy on seizure-induced BDNF expression in rat hippocampus. Brain Res. Mol. Brain Res. 55, 81–91.
Lechan, R.M., Toni, R., Clark, B.D., Cannon, J.G., Shaw, A.R., Dinarello, C.A., Reichlin, S., 1990. Immunoreactive interleukin-1 beta localization in the rat forebrain. Brain Res. 514, 135–140.
Lee, R., Kermani, P., Teng, K.K., Hempstead, B.L., 2001. Regulation of cell survival by secreted proneurotrophins. Science 294, 1945–1948.
Lu, B., 2003. BDNF and activity-dependent synaptic modulation. Learn Mem. 10, 86–98.
Lu, B., Pang, P.T., Woo, N.H., 2005. The yin and yang of neurotrophin action. Nat. Rev. Neurosci. 6, 603–614.
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, 635–646.
Lynch, M.A., 2010. Age-related neuroinflammatory changes negatively impact on neuronal function. Front. Aging Neurosci. 1, 6.
Lynch, M.A., 2014. Neuroinflammatory changes negatively impact on LTP: a focus on IL-1beta. Brain Res..
Maier, S.F., Watkins, L.D., Nance, D.M., 2001. Multiple routes of action of interleukin-1 on the nervous system. In: Ader, R., Felton, D.L., Cohen, N. (Eds.), Psychoneuroimmunology. Academic Press, New York, pp. 563–583.
Mallat, M., Houlgatte, R., Brachet, P., Prochiantz, A., 1989. Lipopolysaccharide-stimulated rat brain macrophages release NGF in vitro. Dev. Biol. 133, 309–311.
Matsumoto, T., Rauskolb, S., Polack, M., Klose, J., Kolbeck, R., Korte, M., Barde, Y.A., 2008. Biosynthesis and processing of endogenous BDNF: CNS neurons store and secrete BDNF, not pro-BDNF. Nat. Neurosci. 11, 131–133.
McAllister, A.K., Katz, L.C., Lo, D.C., 1999. Neurotrophins and synaptic plasticity. Annu Rev. Neurosci. 22, 295–318.
McCusker, J., Cole, M., Dendukuri, N., Belzile, E., Primeau, F., 2001. Delirium in older medical inpatients and subsequent cognitive and functional status: a prospective study. CMAJ 165, 575–583.
Medzhitov, R., 2008. Origin and physiological roles of inflammation. Nature 454, 428–435.
Metsis, M., Timmusk, T., Arenas, E., Persson, H., 1993. Differential usage of multiple brain-derived neurotrophic factor promoters in the rat brain following neuronal activation. Proc. Natl. Acad. Sci. U. S. A. 90, 8802–8806.
Min, S.S., Quan, H.Y., Ma, J., Han, J.S., Jeon, B.H., Seol, G.H., 2009. Chronic brain inflammation impairs two forms of long-term potentiation in the rat hippocampal CA1 area. Neurosci. Lett. 456, 20–24.
Mittelbronn, M., 2014. The M1/M2 immune polarization concept in microglia: a fair transfer? Neuroimmunol. Neuroinflamm. 1, 6–7.
Morris, G.P., Clark, I.A., Zinn, R., Vissel, B., 2013. Microglia: a new frontier for synaptic plasticity, learning and memory, and neurodegenerative disease research. Neurobiol. Learn Mem. 105, 40–53.
Morris, R., 1984. Developments of a water-maze procedure for studying spatial learning in the rat. J. Neurosci. Methods 11, 47–60.
Murray, C.A., Lynch, M.A., 1998. 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, 2974–2981.
Nakajima, K., Tohyama, Y., Kohsaka, S., Kurihara, T., 2002. Ceramide activates microglia to enhance the production/secretion of brain-derived neurotrophic factor (BDNF) without induction of deleterious factors in vitro. J. Neurochem. 80, 697–705.
Nakayama, M., Gahara, Y., Kitamura, T., Ohara, O., 1994. Distinctive four promoters collectively direct expression of brain-derived neurotrophic factor gene. Brain Res. Mol. Brain Res. 21, 206–218.
Nguyen, M.D., Julien, J.P., Rivest, S., 2002. Innate immunity: the missing link in neuroprotection and neurodegeneration? Nat. Rev. Neurosci. 3, 216–227.
Nimmerjahn, A., Kirchhoff, F., Helmchen, F., 2005. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science 308, 1314–1318.
Nistico, R., Mango, D., Mandolesi, G., Piccinin, S., Berretta, N., Pignatelli, M., Feligioni, M., Musella, A., Gentile, A., Mori, F., Bernardi, G., Nicoletti, F., Mercuri, N.B., Centonze, D., 2013. Inflammation subverts hippocampal synaptic plasticity in experimental multiple sclerosis. PLoS One 8, e54666.
Norden, D.M., Godbout, J.P., 2013. Review: microglia of the aged brain: primed to be activated and resistant to regulation. Neuropathol. Appl. Neurobiol. 39, 19–34.
Oitzl, M.S., van Oers, H., Schobitz, B., de Kloet, E.R., 1993. Interleukin-1 beta, but not interleukin-6, impairs spatial navigation learning. Brain Res. 613, 160–163.
Oliff, H.S., Berchtold, N.C., Isackson, P., Cotman, C.W., 1998. Exercise-induced regulation of brain-derived neurotrophic factor (BDNF) transcripts in the rat hippocampus. Brain Res. Mol. Brain Res. 61, 147–153.
Pandharipande, P., Jackson, J., Ely, E.W., 2005. Delirium: acute cognitive dysfunction in the critically ill. Curr. Opin. Crit. Care 11, 360–368.
Pang, P.T., Lu, B., 2004. Regulation of late-phase LTP and long-term memory in normal and aging hippocampus: role of secreted proteins tPA and BDNF. Ageing Res. Rev. 3, 407–430.
Paolicelli, R.C., Bolasco, G., Pagani, F., Maggi, L., Scianni, M., Panzanelli, P., Giustetto, M., Ferreira, T.A., Guiducci, E., Dumas, L., Ragozzino, D., Gross, C.T., 2011. Synaptic pruning by microglia is necessary for normal brain development. Science 333, 1456–1458.
Parkhurst, C.N., Yang, G., Ninan, I., Savas, J.N., Yates 3rd, J.R., Lafaille, J.J., Hempstead, B.L., Littman, D.R., Gan, W.B., 2013. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell 155, 1596–1609.
Perry, V.H., 2004. The influence of systemic inflammation on inflammation in the brain: implications for chronic neurodegenerative disease. Brain Behav. Immun. 18, 407–413.
Perry, V.H., Cunningham, C., Holmes, C., 2007. Systemic infections and inflammation affect chronic neurodegeneration. Nat. Rev. Immunol. 7, 161–167.
Perry, V.H., Holmes, C., 2014. Microglial priming in neurodegenerative disease. Nat. Rev. Neurol. 10, 217–224.
Perry, V.H., Matyszak, M.K., Fearn, S., 1993. Altered antigen expression of microglia in the aged rodent CNS. Glia 7, 60–67.
Phillips, H.S., Hains, J.M., Armanini, M., Laramee, G.R., Johnson, S.A., Winslow, J.W., 1991. BDNF mRNA is decreased in the hippocampus of individuals with Alzheimer's disease. Neuron 7, 695–702.
Phillips, R.G., LeDoux, J.E., 1992. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav. Neurosci. 106, 274–285.
Prinz, M., Priller, J., 2014. Microglia and brain macrophages in the molecular age: from origin to neuropsychiatric disease. Nat. Rev. Neurosci. 15, 300–312.
Pugh, C.R., Nguyen, K.T., Gonyea, J.L., Fleshner, M., Wakins, L.R., Maier, S.F., Rudy, J.W., 1999. Role of interleukin-1 beta in impairment of contextual fear conditioning caused by social isolation. Behav. Brain Res. 106, 109–118.
Quan, N., Banks, W.A., 2007. Brain-immune communication pathways. Brain Behav. Immun. 21, 727–735.
Raivich, G., 2005. Like cops on the beat: the active role of resting microglia. Trends Neurosci. 28, 571–573.
Ransohoff, R.M., Brown, M.A., 2012. Innate immunity in the central nervous system. J. Clin. Investig. 122, 1164–1171.
Ransohoff, R.M., Perry, V.H., 2009. Microglial physiology: unique stimuli, specialized responses. Annu Rev. Immunol. 27, 119–145.
Rapp, P.R., Gallagher, M., 1996. Preserved neuron number in the hippocampus of aged rats with spatial learning deficits. Proc. Natl. Acad. Sci. U. S. A. 93, 9926–9930.
Rapp, P.R., Stack, E.C., Gallagher, M., 1999. Morphometric studies of the aged hippocampus: I. Volumetric analysis in behaviorally characterized rats. J. Comp. Neurol. 403, 459–470.
Rathinam, V.A., Vanaja, S.K., Fitzgerald, K.A., 2012. Regulation of inflammasome signaling. Nat. Immunol. 13, 333–342.
Rauskolb, S., Zagrebelsky, M., Dreznjak, A., Deogracias, R., Matsumoto, T., Wiese, S., Erne, B., Sendtner, M., Schaeren-Wiemers, N., Korte, M., Barde, Y.A., 2010. Global deprivation of brain-derived neurotrophic factor in the CNS reveals an area-specific requirement for dendritic growth. J. Neurosci. 30, 1739–1749.
Rogers, J., Luber-Narod, J., Styren, S.D., Civin, W.H., 1988. Expression of immune system-associated antigens by cells of the human central nervous system: relationship to the pathology of Alzheimer's disease. Neurobiol. Aging 9, 339–349.
Rosch, H., Schweigreiter, R., Bonhoeffer, T., Barde, Y.A., Korte, M., 2005. The neurotrophin receptor p75NTR modulates long-term depression and regulates the expression of AMPA receptor subunits in the hippocampus. Proc. Natl. Acad. Sci. U. S. A. 102, 7362–7367.
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, 61–67.
Russo-Neustadt, A.A., Alejandre, H., Garcia, C., Ivy, A.S., Chen, M.J., 2004. Hippocampal brain-derived neurotrophic factor expression following treatment with reboxetine, citalopram, and physical exercise. Neuropsychopharmacology 29, 2189–2199.
Schafer, D.P., Lehrman, E.K., Kautzman, A.G., Koyama, R., Mardinly, A.R., Yamasaki, R., Ransohoff, R.M., Greenberg, M.E., Barres, B.A., Stevens, B., 2012. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron 74, 691–705.
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, 7778–7783.
Schuman, E.M., Dynes, J.L., Steward, O., 2006. Synaptic regulation of translation of dendritic mRNAs. J. Neurosci. 26, 7143–7146.
Selkoe, D.J., 2002. Alzheimer's disease is a synaptic failure. Science 298, 789–791.
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.
Smith, D.M., Mizumori, S.J., 2006. Hippocampal place cells, context, and episodic memory. Hippocampus 16, 716–729.
Smith, T.D., Adams, M.M., Gallagher, M., Morrison, J.H., Rapp, P.R., 2000. Circuit-specific alterations in hippocampal synaptophysin immunoreactivity predict spatial learning impairment in aged rats. J. Neurosci. 20, 6587–6593.
Song, C., Zhang, Y., Dong, Y., 2013. Acute and subacute IL-1beta administrations differentially modulate neuroimmune and neurotrophic systems: possible implications for neuroprotection and neurodegeneration. J. Neuroinflamm. 10, 59.
Squire, L.R., Stark, C.E., Clark, R.E., 2004. The medial temporal lobe. Annu Rev. Neurosci. 27, 279–306.

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Streit, W.J., Braak, H., Xue, Q.S., Bechmann, I., 2009. Dystrophic (senescent) rather than activated microglial cells are associated with tau pathology and likely precede neurodegeneration in Alzheimer's disease. Acta Neuropathol. 118, 475–485.

Streit, W.J., Xue, Q.S., 2009. Life and death of microglia. J. Neuroimmune Pharmacol. 4, 371–379.

Streit, W.J., Xue, Q.S., 2012. Alzheimer's disease, neuroprotection, and CNS immunosenescence. Front. Pharmacol. 3, 138.

Suzuki, H., Imai, F., Kanno, T., Sawada, M., 2001. Preservation of neurotrophin expression in microglia that migrate into the gerbil's brain across the blood-brain barrier. Neurosci. Lett. 312, 95–98.

Takao, T., Tracey, D.E., Mitchell, W.M., De Souza, E.B., 1990. Interleukin-1 receptors in mouse brain: characterization and neuronal localization. Endocrinology 127, 3070–3078.

Tanaka, J., Horiike, Y., Matsuzaki, M., Miyazaki, T., Ellis-Davies, G.C., Kasai, H., 2008. Protein synthesis and neurotrophin-dependent structural plasticity of single dendritic spines. Science 319, 1683–1687.

Tapia-Arancibia, L., Aliaga, E., Silhol, M., Arancibia, S., 2008. New insights into brain BDNF function in normal aging and Alzheimer disease. Brain Res. Rev. 59, 201–220.

Taylor, A.R., Gifondorwa, D.J., Robinson, M.B., Strupe, J.L., Prevette, D., Johnson, J.E., Hempstead, B., Oppenheim, R.W., Milligan, C.E., 2012. Motoneuron programmed cell death in response to proBDNF. Dev. Neurobiol. 72, 699–712.

Teng, H.K., Teng, K.K., Lee, R., Wright, S., Tevar, S., Almeida, R.D., Kermani, P., Torkin, R., Chen, Z.Y., Lee, F.S., Kraemer, R.T., Nykjaer, A., Hempstead, B.L., 2005. ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. J. Neurosci. 25, 5455–5463.

Timmusk, T., Palm, K., Metsis, M., Reintam, T., Paalme, V., Saarma, M., Persson, H., 1993. Multiple promoters direct tissue-specific expression of the rat BDNF gene. Neuron 10, 475–489.

Tombaugh, G.C., Rowe, W.B., Chow, A.R., Michael, T.H., Rose, G.M., 2002. Theta-frequency synaptic potentiation in CA1 in vitro distinguishes cognitively impaired from unimpaired aged Fischer 344 rats. J. Neurosci. 22, 9932–9940.

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, 17714–17724.

Tremblay, M.E., Lowery, R.L., Majewska, A.K., 2010. Microglial interactions with synapses are modulated by visual experience. PLoS Biol. 8, e1000527.

Tyler, W.J., Alonso, M., Bramham, C.R., Pozzo-Miller, L.D., 2002. From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. Learn Mem. 9, 224–237.

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, 26252–26258.

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, 6811–6819.

Viviani, B., Bartesaghi, S., Gardoni, F., Vezzani, A., Behrens, M.M., Bartfai, T., Binaglia, M., Corsini, E., Di Luca, M., Galli, C.L., Marinovich, M., 2003. Interleukin-1beta enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases. J. Neurosci. 23, 8692–8700.

Viviani, B., Boraso, M., 2011. Cytokines and neuronal channels: a molecular basis for age-related decline of neuronal function? Exp. Gerontol. 46, 199–206.

Volosin, M., Song, W., Almeida, R.D., Kaplan, D.R., Hempstead, B.L., Friedman, W.J., 2006. Interaction of survival and death signaling in basal forebrain neurons: roles of neurotrophins and proneurotrophins. J. Neurosci. 26, 7756–7766.

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

Wofford, J.L., Loehr, L.R., Schwartz, E., 1996. Acute cognitive impairment in elderly ED patients: etiologies and outcomes. Am. J. Emerg. Med. 14, 649–653.

Wong, W.T., 2013. Microglial aging in the healthy CNS: phenotypes, drivers, and rejuvenation. Front. Cell. Neurosci. 7, 22.

Woo, N.H., Teng, H.K., Siao, C.J., Chiaruttini, C., Pang, P.T., Milner, T.A., Hempstead, B.L., Lu, B., 2005. Activation of p75NTR by proBDNF facilitates hippocampal long-term depression. Nat. Neurosci. 8, 1069–1077.

Wynne, A.M., Henry, C.J., Godbout, J.P., 2009. Immune and behavioral consequences of microglial reactivity in the aged brain. Integr. Comp. Biol. 49, 254–266.

Xing, B., Bachstetter, A.D., Van Eldik, L.J., 2011. Microglial p38alpha MAPK is critical for LPS-induced neuron degeneration, through a mechanism involving TNFalpha. Mol. Neurodegener. 6, 84.

Yang, J., Siao, C.J., Nagappan, G., Marinic, T., Jing, D., McGrath, K., Chen, Z.Y., Mark, W., Tessarollo, L., Lee, F.S., Lu, B., Hempstead, B.L., 2009. Neuronal release of proBDNF. Nat. Neurosci. 12, 113–115.

Yirmiya, R., Goshen, I., 2011. Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain Behav. Immun. 25, 181–213.

Zagrebelsky, M., Holz, A., Dechant, G., Barde, Y.A., Bonhoeffer, T., Korte, M., 2005. The p75 neurotrophin receptor negatively modulates dendrite complexity and spine density in hippocampal neurons. J. Neurosci. 25, 9989–9999.

Zhan, Y., Paolicelli, R.C., Sforazzini, F., Weinhard, L., Bolasco, G., Pagani, F., Vyssotski, A.L., Bifone, A., Gozzi, A., Ragozzino, D., Gross, C.T., 2014. Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. Nat. Neurosci. 17, 400–406.

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