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# Immune modulation of learning, memory, neural plasticity and neurogenesis

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ABSTRACT

Over the past two decades it became evident that the immune system plays a central role in modulating learning, memory and neural plasticity. Under normal quiescent conditions, immune mechanisms are activated by environmental/psychological stimuli and positively regulate the remodeling of neural circuits, promoting memory consolidation, hippocampal long-term potentiation (LTP) and neurogenesis. These beneficial effects of the immune system are mediated by complex interactions among brain cells with immune functions (particularly microglia and astrocytes), peripheral immune cells (particularly T cells and macrophages), neurons, and neural precursor cells. These interactions involve the responsiveness of non-neuronal cells to classical neurotransmitters (e.g., glutamate and monoamines) and hormones (e.g., glucocorticoids), as well as the secretion and responsiveness of neurons and glia to low levels of inflammatory cytokines, such as interleukin (IL)-1, IL-6, and TNFα, as well as other mediators, such as prostaglandins and neurotrophins. In conditions under which the immune system is strongly activated by infection or injury, as well as by severe or chronic stressful conditions, glia and other brain immune cells change their morphology and functioning and secrete high levels of pro-inflammatory cytokines and prostaglandins. The production of these inflammatory mediators disrupts the delicate balance needed for the neurophysiological actions of immune processes and produces direct detrimental effects on memory, neural plasticity and neurogenesis. These effects are mediated by inflammation-induced neuronal hyper-excitability and adrenocortical stimulation, followed by reduced production of neurotrophins and other plasticity-related molecules, facilitating many forms of neuropathology associated with normal aging as well as neurodegenerative and neuropsychiatric diseases.



It is now firmly established that the immune system can modulate brain functioning and behavioral processes. This modulation is exerted by communication pathways from the peripheral immune system to the brain as well as by signals produced by immune-like processes involving neuro–glial communication within the brain. Behavioral and neural plasticity are among the most important aspects of brain functioning that are modulated by immune mechanisms. The aim of the present review is to present a comprehensive and integrative view of the complex dual role of the immune system in learning, memory, neural plasticity and neurogenesis. The first part of the review will focus on the physiological beneficial effects of the immune system under normal, quiescent conditions. Under such conditions, immune mechanisms are activated by environmental/psychological stimuli and positively regulate neuroplasticity and neurogenesis, promoting learning, memory, and hippocampal long-term potentiation (LTP). The second part of the review will focus on the detrimental effects of inflammatory conditions induced by infections and injury as well as severe or chronic stress, demonstrating that under such conditions the delicate physiological balance between immune and neural processes is disrupted, resulting in neuronal hyper-excitability, hormonal aberrations, reduced neurotrophic factors production and suppressed neurogenesis, leading to impairments in learning, memory and neuroplasticity.

## 1. The role of the immune system in learning, memory, neural plasticity and neurogenesis under quiescent conditions

The immune system is primarily involved in surveillance of bodily tissues and protection from infectious agents and various forms of injury. It is also activated by, and participates in processes that prepare the tissues for potential danger of such challenges. In addition, immune-like processes are involved in tissue remodeling, which is a continuous process of dynamic alterations in a specific tissue or a whole organ that facilitates morphological and functional adaptations to the ever changing environmental demands. For example, in the bones macrophage-like cells (osteoclasts) continuously regulate bone structure and function by tissue resorption and by secreting myriad cytokines and chemokines that adapt the bone to internal and external pressures and demands (Teitelbaum, 2000). Interestingly, osteoclasts (and other bone cells)

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do not function autonomously, but are importantly influenced by the endocrine and nervous systems, demonstrating the importance of neuro–immune interactions for tissue maintenance and remodeling even in conditions that do not involve infection or injury (Bajayo et al., 2005; Yirmiya and Bab, 2009; Yirmiya et al., 2006). Similar immune-mediated remodeling processes also occur in other tissues, such as the muscles, fat, and reproductive organs, particularly when these tissues encounter and have to adapt to major environmental challenges, e.g., during or following muscle exertion, obesity, ovulation, and menses.

The healthy brain provides a classic example for the necessity of tissue remodeling to adaptive coping, since neural cells and networks are constantly altered by experience. During development, neurons and other cells are added to the evolving brain structures, however, many other cells (as much as 50–60% of the neurons that are formed in the brain during development) die before birth (Oppenheim, 1991). Moreover, a large percentage of the processes of the developing neurons undergo dynamic and dramatic pruning, i.e., selective degeneration of whole or parts of the dendrites, axon collaterals or terminals. Neuronal (and other cellular) death and pruning ensures the formation of accurate, fine-tuned, and efficiently functioning neural circuits (Luo and O'Leary, 2005). In animals and humans these processes continue into adulthood, albeit in a less dramatic manner, i.e., brain cells still undergo apoptosis and neurogenesis (at least in specific brain locations), axons and dendrites are still formed and get pruned, and most importantly, individual synapses (and associated structural elements) are formed, retracted and get modified throughout life (Luo and O'Leary, 2005). These processes, collectively termed neural plasticity, underlie the most amazing and wonderful capacity of the brain to adapt to the ever changing environment via learning and memory.

Similarly to its role in remodeling of bodily tissues, the immune system participates in modulating and sculpting the brain. It has to be particularly involved when cellular events in the nervous system lead to apoptosis, as well as degradation of processes and even individual synapses. Cellular corpses, neuritic debris, and remains of other cells (e.g., myelin and associated proteins that remain after normal pruning of axonal processes) cannot stay in the tissue without interfering with its normal functioning. Therefore, the process of neural plasticity must be exquisitely coordinated with and regulated by immune mechanisms that ensure the quality and efficiency of this process. As will be discussed below, immune-mediated brain remodeling processes may be initiated by neuronal activity, but they primarily involve various non-neuronal cells within the brain parenchyma (mainly microglia, but also astrocytes and possibly mast cells), as well as cells within and around the brain vasculature, choroids plexus and meninges (including endothelial cells, perivascular macrophages, and T cells). Other immune molecules that were also found to be important for normal neural and synaptic functioning include the major histocompatibility complex (MHC) class I (Boulanger and Shatz, 2004), and the complement system (Stevens et al., 2007). Together, the brain-associated immune cells and the molecules secreted by these cells take part in promoting plasticity-related structural changes, and may be directly involved in the neurophysiological processes underlying the plastic changes.

Interestingly, the activation of neuroimmune responses by physiological neural activity (in the absence of infection or overt injury) can also activate brain-to-body communication pathways, such as the hypothalamus–pituitary–adrenal (HPA) axis and the autonomic nervous system (Besedovsky and Del Rey, 2007). The resultant peripheral hormonal and neurochemical alterations (e.g., the elevation in blood levels of glucocorticoids, adrenaline and norepinephrine) feed back into the brain and exert powerful modulatory effects on neural plasticity and neurogenesis. These neuro-hormonal processes can also involve alterations in peripheral immune parameters, which in turn influence central immune responses, creating a brain-to-body-to-brain reverberating feedback loops.

The idea that the immune system is involved in normal neurobehavioral processes was suggested more than a decade ago, although initially it did not receive much attention, probably because of the overwhelming evidence demonstrating that immune processes during infection, injury and stress produce sickness behavior, debilitation and impaired neurobehavioral plasticity. Based on the observations that cytokines and their receptors are expressed, albeit at low levels, in the healthy brain, that neurons (in addition to glia) can produce and respond to inflammatory cytokines, and that neuronal activity can regulate the production and secretion of cytokines, it was suggested that cytokines act as neuromodulators in the normal healthy brain (i.e., without any overt pathophysiological stimuli) (Vitkovic et al., 2000). Additional support for this notion came from studies demonstrating the involvement of cytokines in specific normal neurobehavioral functions, including sleep (Krueger et al., 2001; Opp, 2005), pain (Wolf et al., 2003) and responsiveness to various psychological stressors (Goshen and Yirmiya, 2009). The following section demonstrates that immune processes and particularly pro-inflammatory cytokines play an important role in behavioral and neural plasticity.

### 1.1. The role of the immune system in promoting learning and memory

#### 1.1.1. The role of T cells

Based on their previous findings that CD4+ T cells targeted against brain self antigens can be neuroprotective (a phenomenon termed 'protective autoimmunity') (Moalem et al., 1999), M. Schwartz, J. Kipnis and their colleagues raised the notion that circulating T cells play a general supportive role in brain and mind functioning, including cognitive abilities and neurogenesis (Kipnis et al., 2008; Schwartz and Shechter, 2010). Experimental evidence for this notion was first provided by demonstrating that mice with severe combined immune deficiency (SCID, devoid of both T and B cells) as well as nude mice (deficient only in mature T cells) display dramatic impairments in hippocampal-dependent spatial learning and memory in the water maze (Kipnis et al., 2004; Ron-Harel et al., 2008). SCID mice also exhibited impaired learning and memory in three other paradigms measuring hippocampal functioning – the water-free Barnes maze, the radial arm water maze (Brynskikh et al., 2008) and recognition of novel spatial arrangement of familiar objects (Ron-Harel et al., 2008). Furthermore, replenishing T cells in nude mice markedly improved their learning and memory in the water maze. Consistently, boosting T cell activation by vaccination with copolymer-1, a weak agonist of various self-reactive T cells, counteracted learning deficits induced by neurotransmitter abnormalities (Kipnis et al., 2004). Replenishment with T cells derived from wild type (WT) mice (but not with SCID-derived T cells or with T-cell depleted splenocytes) also improved the memory of SCID mice in the water maze (Ron-Harel et al., 2008) or the radial arm water maze (Brynskikh et al., 2008). A recent study corroborated these findings by demonstrating that T cell depleted mice displayed impaired performance in reversal training in the water maze paradigm (although their performance during the learning phase or the probe test was similar to control) (Wolf et al., 2009a).

The learning and memory impairments in SCID mice do not result from health problems related to their lifelong immune deficiency – following complete depletion of their immune system by lethal irradiation, adult SCID mice that received bone marrow transplantation of WT immune cells exhibited normal memory functioning in the water maze and the novel location task, whereas mice transplanted with bone marrow cells derived from SCID mice

exhibited marked memory deficits (Brynskikh et al., 2008; Ron-Harel et al., 2008). Consistent with all of the above findings, transgenic mice with excess of monospecific T cells directed towards a brain antigen exhibited better learning and memory in the water maze than their controls, whereas the performance of mice with transgenic excess of T cells directed against an irrelevant (non-self) antigen was worse than their WT controls (Ziv et al., 2006).

The meningeal spaces constitute an important location for T cell-based support of behavioral plasticity, providing an explanation for such effects of T cells without their presence in the CNS parenchyma (Derecki et al., 2010; Schwartz and Shechter, 2010). Specifically, performance of cognitive tasks led to increased number of T cells in the meninges, and depletion of T cells from meningeal spaces resulted in learning and memory impairments. Moreover, this depletion skewed meningeal myeloid cells toward a pro-inflammatory phenotype, which may have interfered with the learning process (Derecki et al., 2010). The study further demonstrates an important role for T cell-derived IL-4 in the regulation of cognitive functioning. Specifically, the T cells that accumulated in the meninges following learning in the water maze expressed high levels of IL-4. Furthermore, IL-4-deficient mice, as well as irradiated wild-type recipient mice that were transplanted with IL-4-deficient bone marrow, exhibited cognitive impairments, concomitantly with a skewed pro-inflammatory meningeal myeloid cell phenotype. Moreover, adoptive transfer of T cells from wild-type into IL-4-deficient mice reversed cognitive impairment and attenuated the pro-inflammatory character of meningeal myeloid cells. Thus, this study clearly demonstrates that T cell-derived IL-4 regulates learning and memory, possibly by influencing meningeal myeloid cell activation (Derecki et al., 2010).

The importance of properly functional and regulated T cell immunity in cognitive functioning is supported not only by the above-mentioned studies on SCID, nude and irradiated/immune-depleted mice, but also by more common and natural conditions associated with both diminished T cell activity and cognitive impairments, such as aging, HIV infection and chemotherapy (Kipnis et al., 2008; Ron-Harel and Schwartz, 2009). Indeed, manipulation of T cells in aged mice (e.g., bone marrow transplantation following irradiation) reversed some aspects of the spatial memory deficits exhibited by these animals (Ron-Harel et al., 2008). Moreover, the procedures that have so far been shown to alleviate brain aging and the associated memory loss, including physical exercise and calorie restriction, enhance T cell immunity, suggesting that boosting T cell immunity might be beneficial for aging-associated memory impairments (Ron-Harel and Schwartz, 2009).

### 1.1.2. The role of inflammatory cytokines

Most of the research on the role of the immune system in learning and memory processes focused on the involvement of inflammatory cytokines, particularly IL-1, IL-6, and tumor necrosis factor TNF-α.

*1.1.2.1. IL-1.* Several lines of evidence indicate that IL-1 is required for some learning and memory processes, particularly for the consolidation of memory that depends on proper functioning of the hippocampus:

*1.1.2.1.1. Induction of IL-1 during the learning process.* Since under normal quiescent conditions brain levels of IL-1 are very low (usually at or below the threshold of IL-1 protein detection), IL-1 should be induced during learning and memory consolidation in order to exert effects on these processes. We assessed this hypothesis by measuring the expression of IL-1β mRNA at various time points following contextual fear conditioning. We reported that IL-1β gene expression in the hippocampus showed a significant increase 24 h, but not 1.5 or 4 h after contextual learning (Goshen et al., 2007). This increase could not be attributed to the exposure to the stress caused by the electrical shock per se, but only to the learning experience, as shock administration in the home cage did not affect IL-1β gene expression. Interestingly, in two genetically manipulated mouse strains with deficient IL-1 signaling, mice with deletion of the IL-1 receptor type I (IL-1rKO) or mice with transgenic over-expression of IL-1 receptor antagonist (IL-1raTG), the levels of IL-1β gene expression were not increased 24 h after fear-conditioning. Because IL-1 itself is one of the major triggers for the induction of further IL-1 production (Dinarello, 1996), it is possible that an initial small increase in IL-1 secretion and activation of IL-1R1 are required to induce the relatively high levels of expression at 24 h post-conditioning. A recent study corroborated these findings by demonstrating the induction of IL-1β mRNA expression following spontaneous spatial recognition in the Y-maze paradigm (Labrousse et al., 2009). Interestingly, mice with genetic deletion of P2X7 ATP receptors, which are critical for IL-1β production by hippocampal glia, displayed no IL-1β expression following exposure to this paradigm, concomitantly with memory impairment and abrogation of hippocampal neural activation. These findings support a crucial role for P2X7 receptor-mediated IL-1β expression in memory processes involving the hippocampus (Labrousse et al., 2009). In another study, the gene expression of IL-1α, IL-1β, and IL-1ra was examined in the hippocampus at different time points (1, 4, 6, and 9 h) following a single acquisition trial of step-down passive-avoidance. In that study, IL-1α gene expression was increased 4 h after acquisition, but no change in the expression of IL-1β and IL-1ra were observed at any time point (Depino et al., 2004). The somewhat different results obtained in this study may stem from a procedural difference because the control group in this study consisted of animals that received a shock in the conditioning context but did not perform the step-down action, thus the difference between the experimental and control groups is not in contextual learning per se, but in its association with the performance of a motor activity.

*1.1.2.1.2. Facilitation of learning and memory by IL-1 administration.* Although under most circumstances exogenous administration of IL-1 produces learning and memory impairments (see Section 2.1.1.1 below), in other situations (which probably depend on specific combinations of the timing, dose and route of administration, as well as on the particular memory paradigm), administration of IL-1 produces memory facilitation.

Clear evidence for IL-1-induced memory facilitation was obtained using the passive and active avoidance paradigms. In one study, we demonstrated that i.c.v. administration of a relatively low dose of IL-1β, immediately following passive avoidance training, resulted in better memory 5–8 days later (Yirmiya et al., 2002). This finding was later corroborated by showing that i.c.v. administration of IL-1β shortly before passive avoidance acquisition, as well as before the memory tests (conducted 24 and 48 h later) resulted in improved memory (Song et al., 2003). Although in another study very low doses of IL-1α had no effect on passive avoidance memory, similar doses of IL-1α attenuated the amnesic effect of scopolamine (an anti-cholinergic drug) on memory in this test (Bianchi et al., 1998). In the active avoidance paradigm, in which rats can press a lever to prevent an imminent shock (avoidance response) or to terminate the shock after it had begun (escape response), low doses of IL-1β, administered 24 h before training, increased the number of avoidance responses (which critically depend on hippocampal functioning), but had no effect on the number of escape responses (which are hippocampal-independent) (Brennan et al., 2003, 2004).

Under some conditions, IL-1β was also found to facilitate spatial and contextual fear memories, which also depend on hippocampal functioning. In one study, IL-1β administration facilitated spatial memory in the water maze (Gibertini, 1998). In another study, we found that i.c.v. administration of a relatively low dose of

IL-1β immediately following the association of a specific context with mild foot-shock improved contextual fear conditioning, tested 48 h later (Goshen et al., 2007). The same IL-1 dose had no effect on auditory cued fear conditioning, which does not depend on hippocampal functioning. Finally, peripheral treatment with IL-β led to facilitated acquisition of the classically conditioned eye blink response (Servatius and Beck, 2003).

*1.1.2.1.3. Learning and memory are impaired following pharmacological blockade of IL-1 signaling via IL-1ra administration.* The effects of IL-1ra were studied in several memory paradigms. In the passive avoidance paradigm, intracerebral administration of IL-1ra at the end of training significantly impaired memory, tested 5–8 days later (Yirmiya et al., 2002). In the fear conditioning paradigm, similar administration of IL-1ra also induced contextual (but not auditory-cued) fear conditioning impairment (Goshen et al., 2007). It should be noted that in contrast with these findings, intra-hippocampal injection of an adenovector containing the rat IL-1ra gene was found to enhance short- and long-term memory in the step-down passive avoidance test (Depino et al., 2004). The use of an adenovector vs. pharmacological IL-1ra administration, and differences in the species (mice vs. rats) and learning procedures may explain the discrepancy between the results of these studies.

*1.1.2.1.4. Learning and memory are disturbed in mice with genetic impairments in IL-1 signaling.* To corroborate the studies demonstrating that pharmacological blockade of IL-1 impairs memory functioning, we examined spatial memory and fear conditioning in IL-1rKO and IL-1raTG mice. In both models, IL-1 signaling is completely abolished, as reflected by lack of responsiveness to exogenous IL-1α or IL-1β administration. Both IL-1rKO and IL-1raTG mice displayed a slower rate of learning in the spatial memory paradigm (Avital et al., 2003; Goshen et al., 2007). In contrast, in the non-spatial memory paradigm (visible platform) both IL-1-signaling deficient strains showed no differences from controls. Similar findings were obtained using the fear conditioning paradigm: both IL-1rKO and IL-1raTG mice exhibited impaired contextual, but normal auditory-cued fear conditioning (Avital et al., 2003; Goshen et al., 2009, 2007). A recent study, corroborated these findings, demonstrating that IL-1raTG mice displayed learning and long (but not short) term memory deficits in the water T maze paradigm (Spulber et al., 2009), which also depends on hippocampal functioning. Another recent study reported contradictory findings, i.e., increased freezing in both contextual and auditory-cued fear conditioning testing (Koo and Duman, 2009). The reason for this discrepancy is not clear, and may be related to minor procedural and measurement differences, as well as a different genetic background of the mice.

In conclusion, the data presented above demonstrates that IL-1 is induced within the hippocampus during the learning process, that under some conditions exogenous administration of low doses of IL-1 can improve hippocampal-dependent memory functioning, whereas blockade of IL-1 signaling, either by pharmacological or by genetic manipulations, can impair memory functioning. Thus, it can be concluded that low, "physiological" levels of IL-1 in the hippocampus play an important role in learning and memory processes.

*1.1.2.2. IL-6.* Ample research indicates that high levels of IL-6, particularly in the context of aging, are associated with poor memory functioning or memory decline over time (see Section 2.1.1.2 below). However, it is now clear that the role of IL-6 in memory is quite complex and that IL-6 may influence learning and memory in different, and even opposite ways under various conditions. In the only study on the effects of exogenous IL-6 on memory functioning in humans, IL-6 was administered to 19 chronic fatigue syndrome (CFS) patients and 10 control subjects, and memory, as well as other neuropsychological functions, was assessed 6.5 h later. Surprisingly, IL-6 did not produce any memory disturbance. In fact, both CFS patients and controls demonstrated improved performance in this test (Arnold et al., 2002). Although the investigators ascribed this improvement to practice effect, it is possible that the improved cognitive functioning was induced by IL-6 (in the absence of a saline-administered control group, it is impossible to distinguish between these two possibilities).

The possibility that under some conditions IL-6 may be associated with protective effects on cognition was suggested by two additional studies in humans, examining the role of IL-6 in systemic lupus erythematosus and surgical patients. In Lupus patients, a negative association between plasma IL-6 and cognitive decline was obtained, i.e., higher levels of IL-6 in the plasma were associated with higher learning scores (Kozora et al., 2001). Similarly, in a recent study examining the effects of surgical stress on immune and cognitive functioning, we found that the elevation in IL-6 levels one day after surgery was inversely associated with cognitive deterioration, i.e., patients with elevated IL-6 levels exhibited smaller declines in declarative memory regardless of interpersonal differences in age, gender, pain experienced, or baseline ability (Shapira-Lichter et al., 2008).

Consistently with these findings, a protective role for IL-6 administration was also found in two studies using animal models. Specifically, i.p. administration of IL-6 partially blocked the effect of the amnesic drug scopolamine in the passive avoidance task (Bianchi et al., 1997; Bianchi et al., 1998). Moreover, chronic administration of IL-6 for a week, commencing 2 h before ischemia, resulted in improved memory in a passive avoidance task at the end of this week (Matsuda et al., 1996).

*1.1.2.3. TNFα.* In addition to the extensive literature on the detrimental effects of TNFα in learning and memory (see Section 2.1.1.1.3), there is some evidence for its beneficial effects under certain conditions. For example, in the passive avoidance paradigm a single i.p. injection of TNFα 24 h before training resulted in increased number of avoidance as well as escape responses (Brennan et al., 2004). TNFα also seems to have a positive effect on the recovery of memory functioning following infection; after surviving pneumococcal meningitis, mice with targeted deletion of the TNFα gene (TNFαKO) mice demonstrated impaired water maze performance compared to surviving WT controls, suggesting a beneficial role for TNFα in memory recovery (Gerber et al., 2004). This finding suggests that similarly to IL-6, when brain homeostasis is maintained TNFα has a detrimental effect on memory processes, whereas when this balance is violated, TNFα may play a protective role.

### *1.1.3. Prostaglandins*

Prostaglandins (PGs) are important inflammatory mediators, synthesized from arachidonic acid by the enzyme cyclooxygenase (COX). Within the brain, PGs are mainly produced following the induction of COX-2, which is expressed in neurons, glia and endothelial cells. Various stimuli can induce COX-2 expression in the brain, including inflammatory challenges, particularly IL-1, as well as synaptic activity (Laflamme et al., 1999; O'Banion et al., 1996). A role for PGs in memory functioning has been suggested by the findings that peripheral or i.c.v. administration of the non-selective COX inhibitors indomethacin and ibuprofen, as well as the selective COX-2 inhibitors NS-398 and celecoxib, impaired spatial but not visually guided water maze performance (Cowley et al., 2008; Shaw et al., 2003; Teather et al., 2002). A similar attenuation of water maze acquisition was found when the COX-2 specific inhibitor celecoxib was administrated directly into the hippocampus (Rall et al., 2003; Sharifzadeh et al., 2005). Furthermore, direct intra-hippocampal administration of the non-selective COX inhib-

itor naproxen significantly impaired memory in the contextual fear conditioning paradigm (Hein et al., 2007). It should be noted, however, that genetic deficiency of either COX-1 or COX-2 had no effect on spatial learning and memory in the water maze (Kelso et al., 2009).

### 1.2. The role of immune processes in the induction and maintenance of neural plasticity and LTP

The idea that synaptic changes underlie experience-induced adaptations in brain and behavior was proposed more than 60 years ago by Donald Hebb, who suggested that the synapse between two neurons is strengthened if they are active simultaneously (Hebb, 1949). Empirical support for this proposal was provided by the demonstration that brief high-frequency stimulation (HFS) of hippocampal afferents resulted in persistent augmentation of their synaptic strength within the dentate gyrus (DG), a phenomenon termed long-term potentiation (LTP) (Bliss and Lomo, 1973). Ample research demonstrated that synaptic plasticity and LTP underlie memory storage in the hippocampus and other brain areas (Lynch, 2004). It should be noted, however, that although synaptic plasticity was proved in many studies to be necessary for learning and memory, it is not clear whether it is sufficient for memory formation (see (Martin et al., 2000), for review).

As will be discussed below, ample evidence demonstrates that immune processes in the brain produce detrimental effects on neural plasticity, specifically by reducing hippocampal LTP induction and maintenance (reviewed in (Goshen and Yirmiya, 2007; Lynch, 2002; O'Connor and Coogan, 1999). However, in 1998 Hugo Besedovsky and his colleagues (Schneider et al., 1998) published a seminal paper, which demonstrated for the first time that an inflammatory-like process (the secretion of the pro-inflammatory cytokine IL-1 in the hippocampus) accompanies LTP induction and is critically involved in maintaining LTP. Since then, many additional studies verified the role of inflammatory cytokines and other inflammatory mediators in normal, physiological neural plasticity.

#### 1.2.1. The role of inflammatory cytokines

*1.2.1.1. IL-1.* As noted above, the finding that IL-1 gene expression is substantially increased concomitantly with the development of LTP provided the first evidence for the involvement of an inflammatory-like process in normal/physiological neural plasticity. The increased IL-1β gene expression commenced rapidly (15 min after stimulation in hippocampal slices and 8 h after LTP induction in freely moving rats), and it was long lasting, specific to potentiation (i.e., was observed only in the stimulated, but not the contralateral, hippocampus) and could be prevented by blockade of potentiation with the NMDA receptor antagonist AP-5 (Balschun et al., 2003; Schneider et al., 1998). A recent study demonstrated that LTP-associated induction of IL-1β expression is not restricted to the hippocampus: HFS to the spinal cord, which induced a robust LTP of C-fiber responses within the dorsal horn, was associated with a significant increase in the expression of mRNA for IL-1β, measured 6 h following HFS administration (Pedersen et al., 2009).

The LTP-associated elevation in IL-1β gene expression seems to play a causal physiological role in LTP maintenance, as blocking IL-1 receptors by i.c.v. administration of IL-1ra 90 min after the induction of LTP impaired its maintenance (Schneider et al., 1998). The effects of IL-1ra administration before LTP induction are less clear; *in vivo* administration of IL-1ra 30 min before stimulation had no effect in one study (Schneider et al., 1998), but in two other studies IL-1ra administration 30 or 60 min before HFS significantly attenuated the initial potentiation and impaired the maintenance of LTP (Loscher et al., 2003; Schmid et al., 2009). The critical role of IL-1 in LTP was also demonstrated in hippocampal slices *in vitro*: Application of IL-1ra 30 min after the induction of LTP in the rat DG *in vitro* reduced synaptic activity back to baseline levels (Coogan et al., 1999), and when IL-1ra was applied to hippocampal sliced in a physiological temperature for 40 min before stimulation, the initial small increase in synaptic activity subsided within 30 min (Ross et al., 2003). The mechanisms underlying the detrimental effect of IL-1ra on LTP were studied using hippocampal synaptosomes preparation (Loscher et al., 2003), revealing decreased glutamate release and increased JNK phosphorylation following exposure to IL-1ra. Interestingly, these effects were not mediated by the IL-1 receptor type I (IL-1RI), as they appeared both in the presence of neutralizing antibodies against IL-1RI, and in synaptosomes prepared from IL-1rKO mice (Loscher et al., 2003).

Using a different approach to study the necessity of physiological IL-1 levels for hippocampal plasticity, we found that anesthetized IL-1rKO mice exhibited no LTP in the DG following HFS of the perforant path (Avital et al., 2003; Goshen et al., 2009). Similarly, a complete absence of LTP was observed in the CA1 region of hippocampal slices taken from IL-1rKO mice compared with WT controls (Avital et al., 2003). In contrast with these findings, no impairment in either LTP or long term depression (LTD) was observed in mice with knockout of the IL-1α and IL-1β genes (Ikegaya et al., 2003). Short-term plasticity was also affected by IL-1 signaling impairment, evidenced by enhanced paired-pulse inhibition in the DG of IL-1rKO mice *in vivo*, and decreased paired-pulse potentiation in hippocampal slices from IL-1rKO mice (Avital et al., 2003).

Together, the increase in IL-1 gene expression following LTP induction, and the blockade of LTP by pharmacological or genetic manipulations in IL-1 signaling demonstrate the requirement of physiological IL-1 levels for the induction and maintenance of LTP.

*1.2.1.2. IL-6.* As detailed below (Section 2.2.1.2), many studies demonstrated a detrimental effect of elevated IL-6 levels on long-term synaptic plasticity. However, recent studies suggest that endogenous IL-6 may actually have a physiological role in LTP inhibition. In one study, a 20-fold increase in IL-6 gene expression was measured 4 h following *in vivo* LTP induction by HFS (Jankowsky et al., 2000). This finding was corroborated by another study, demonstrating increased IL-6 gene expression 8 h after HFS in freely moving rats as well as 1–3 h after HFS in hippocampal slices (Balschun et al., 2004). This increase was found only in rats in which LTP was robust and maintained for 8 h, but not when it subsided within 3 h following HFS. Immunoneutralization of IL-6 by i.c.v. administration of anti-IL-6 antibodies 90 min following the induction of LTP resulted in longer maintenance of LTP; i.e., LTP was still preserved in anti-IL-6 injected rats after it subsided in control rats. In contrast, anti-IL-6 antibodies that were injected 30 min before or 5 min after the induction of LTP had no effect (Balschun et al., 2004), suggesting that IL-6 is selectively involved in a specific phase of LTP consolidation. No other endogenous protein is known to interfere with LTP maintenance in such a late phase, without influencing LTP induction.

The finding that LTP increases IL-6 gene expression, together with the finding of longer preservation of LTP following IL-6 neutralization, suggest that IL-6 may have a physiological role in the termination of LTP.

*1.2.1.3. TNFα.* Several lines of evidence implicate TNFα in synaptic functioning, in general, and in some forms of synaptic plasticity, in particular. Studies in both hippocampal cultures and slices demonstrated that TNFα selectively secreted by astrocytes enhances synaptic efficacy by increasing surface expression of AMPA receptors. Conversely, blocking TNFα signaling by TNF soluble receptors reduces synaptic strength and decreases AMPA expression (Beattie et al., 2002). It should be noted, however, that the newly expressed

AMPA receptors have abnormal stoichiometry, as they lack the GluR2 subunit; thus, they become Ca2+ permeable and may contribute to neurotoxicity (Stellwagen et al., 2005).

TNFα does not seem to be involved in acute plasticity, reflected by the normal LTP exhibited by mice with genetically impaired TNF signaling (Albensi and Mattson, 2000; Kaneko et al., 2008; Stellwagen and Malenka, 2006) (in fact, under certain conditions it has detrimental effects on LTP, see Section 2.2.1.3). Although in one study a role for TNFα in LTD has been suggested by demonstrating that in hippocampal slices low frequency stimulation of Schaffer collateral axons produced LTD in the CA1 synapses of wild-type but not TNF receptor knockout mice (Albensi and Mattson, 2000), in other preparations TNF signaling-deficient mice displayed normal LTD (Kaneko et al., 2008; Stellwagen and Malenka, 2006). In contrast with its questionable role in acute plasticity, a clear role for TNFα has been shown in two forms of long-term plasticity in the adult brain: synaptic scaling and structural plasticity induced in the visual cortex by monocular deprivation.

Synaptic scaling refers to a set of homeostatic plasticity mechanisms that dynamically adjust the strengths in all synapses on a cell in response to prolonged changes in the cell's electrical activity, thereby stabilizing neural networks functioning. A role for TNFα in synaptic scaling was demonstrated by the finding that following chronic blockade of neuronal activity, TNFα is necessary for the increases in surface AMPAR levels and synaptic strength. Furthermore, it was found that the TNFα required for homeostatic synaptic strengthening is exclusively produced by astrocytes (Stellwagen and Malenka, 2006).

Ample studies demonstrate that monocular deprivation in the adult mammalian brain results in weakening and pruning of inputs from the deprived eye, along with a gradual strengthening and expansion of inputs from the open eye (Wiesel, 1982). A role for TNFα in this phenomenon has been demonstrated by showing that mice deficient in TNFα, either by genetic deletion of the TNFα gene or due to pharmacological blockade of TNFα signaling display normal initial loss of deprived-eye responses, but complete absence of subsequent increase in response to the open eye. This mutation also blocks homeostatic synaptic scaling of mEPSCs in visual cortex *in vitro*, without affecting LTP. These findings suggest that TNFα signaling is essential for experience-dependent homeostatic synaptic scaling process (Kaneko et al., 2008).

#### *1.2.2. Prostaglandins*

In accordance with their role in memory functioning, basal levels of PGs also have a role in neural plasticity. This conclusion is based on several lines of research demonstrating that: (1) COX-2 activity is upregulated following HFS that is associated with LTP induction (Yamagata et al., 1993). (2) PGs production by COX-2 can occur in postsynaptic dendritic spines (Kaufmann et al., 1996). (3) Inhibition of COX activity by ibuprofen resulted in impaired hippocampal LTP (Shaw et al., 2003). Furthermore, selective inhibition of COX-2 (but not COX-1) reduced postsynaptic membrane excitability and LTP induction in hippocampal dentate granule neurons. This reduction, as well as the reduction is downstream signaling mechanisms (extracellular signaling-regulated kinase (ERK)-phosphorylation and c-FOS expression) could be completely rescued by exogenous application of $PGE_2$ (Chen et al., 2002; Cowley et al., 2008). These findings indicate that endogenous basal levels of $PGE_2$ resulting from COX-2 but not COX-1 activity are critical for long-term hippocampal synaptic plasticity.

#### *1.2.3. MHC Class I proteins*

MHC Class I (MHC-I) proteins are expressed by almost all nucleated cells of the body, which bind and display endogenous cellular peptides on the membrane surface and thereby permit immune recognition of "self" vs. "non self" (foreign) antigens generated by infected or cancerous tissues. Recent evidence demonstrates that MHC-I proteins, as well as their immunoreceptors, play an important role in the developing nervous system, in which they may be required for the normal elimination of inappropriate projections, similarly to their immunological role (recognition and removal of unwanted cells expressing "non self" antigens). Furthermore, neuronal MHC-I molecules regulate various aspects of basal synaptic functioning (Boulanger, 2009), and have been implicated in neural plasticity. Specifically, mice with genetic deficiency of MHC-I or the MHC-I receptor component, CD3ζ, display enhanced LTP and an absence of LTD in the hippocampus (Boulanger and Shatz, 2004; Huh et al., 2000), as well as lower threshold for induction of LTD in the cerebellum, associated with improved motor learning acquisition (McConnell et al., 2009).

Interestingly, mice lacking the polypeptide DAP12, which is selectively expressed only in microglia, is structurally and functionally related to CD3ζ, and associates with cell-surface receptors like MHC-I, also exhibit enhanced LTP. This enhancement was accompanied by decreases in the expression of the AMPA receptor GluR2 in the postsynaptic densities, as well as decreased synaptic BNDF-tyrosine kinase receptor B (TrkB) signaling (Roumier et al., 2004). These findings suggest that microglial–neuron interaction can be involved in the regulation of synaptic functioning and neural plasticity.

### *1.3. The role of the immune system and inflammatory cytokines in neurogenesis*

In addition to the biochemical and structural processes of synaptic plasticity, the brain is capable of plasticity in the whole neuronal level, i.e., via the formation of new neurons, a process termed neurogenesis (Deng et al., 2010; Leuner and Gould, 2010). In the healthy brain, neurogenesis is restricted to two defined anatomical locations in which stem cells can proliferate and differentiate into neurons and migrate to their final destination – the subventricular zone of the lateral ventricle (SVZ), from which new neurons migrate to the olfactory bulb, and the subgranular zone of the hippocampal DG (SGZ), from which new neurons migrate to the entire DG. Several lines of evidence indicate that neurogenesis plays an important role in learning, memory and neural plasticity (Deng et al., 2010; Leuner and Gould, 2010): (1) Neurogenesis increases following specific forms of learning and memory formation. (2) The rate of neurogenesis and hippocampal-dependent memory formation are positively correlated. (3) Conditions that increase memory abilities, such as environmental enrichment and exercise, also increase neurogenesis. (4) The level of hippocampal neurogenesis plays a role in determination of the hippocampus-dependent period of memory. (5) Ablation of neurogenesis induces learning and memory impairments.

The neurobiological basis for the role of neurogenesis in learning and memory is probably related to the hyper-plasticity exhibited by these cells. Thus, young granule cells in the adult hippocampus exhibit substantially different active and passive membrane properties than mature granule cells, making these cells hyper-excitable. Moreover, associative long-term potentiation can be induced more easily in young neurons than in mature neurons under identical conditions. Thus, newly generated neurons express unique mechanisms to facilitate synaptic plasticity, which may be important for the formation of new memories (Ge et al., 2007; Schmidt-Hieber et al., 2004). Similarly, recently generated adult-born olfactory interneurons undergo different experience-dependent synaptic modifications compared with their pre-existing mature neighbors and provide a possible substrate for adult neurogenesis-dependent olfactory learning (Nissant et al., 2009).

Several studies indicate that various components of the immune system are involved in the process of neurogenesis.

*1.3.1. T cells*

Initial evidence for a role of T cells in neurogenesis was provided by the demonstration that microglia activated by the cytokines IL-4 or low level of IFN-γ, which are known to be produced by T-helper cells, promoted neurogenesis *in vitro* (Butovsky et al., 2006). More direct evidence was provided by the findings that T-cell deficient mice (either SCID or nude) display a severe impairment in neurogenesis within the hippocampus, which can be rescued by adaptive transfer of WT splenocytes (Ziv et al., 2006). Consistently, transgenic mice in which most T cells express a CNS-specific receptor were found to display enhanced neurogenesis, whereas mice with transgenic excess of T cells with a receptor for a non-CNS protein displayed reduced neurogenesis. Moreover, environmental enrichment, which markedly increased the number of new neurons in the hippocampus of WT mice, induced the appearance of T cells in the parenchyma of the hippocampus, but it had no effect on neurogenesis in SCID mice (Ziv et al., 2006).

Two recent studies corroborated these findings by demonstrating that systemic depletion of CD4-positive T lymphocytes (by either genetic or immunological means) led to significantly reduced hippocampal neurogenesis. The specificity of this effect to T helper cells was attested by the findings that no such effect was observed after depletion of CD8 or B cells, and that repopulation of a strain of mice which lacks both T and B cell function with CD4, but not with CD8 cells rescued the suppressed neurogenesis (Wolf et al., 2009a). Furthermore, specific peripheral T-cell activation (by either antigen-induced arthritis in the knee joint or staphylococcus enterotoxin) was found to be associated with a transient increase in hippocampal precursor cell proliferation and neurogenesis (in contrast with innate immune activation by lipopolysaccharide (LPS), which caused neurogenesis suppression) (Wolf et al., 2009b).

*1.3.2. Microglia*

Microglia are now known to play both beneficial, neuroprotective effects, as well as detrimental, neurotoxic effects under various conditions. Although initially microglia were shown to be involved in neurogenesis suppression, it is now clear that under quiescent conditions they play a role in supporting neurogenesis (Ekdahl et al., 2009; Hanisch and Kettenmann, 2007; Ziv and Schwartz, 2008). Evidence for a beneficial role of microglia in neurogenesis was first provided by showing that exposure of rats to environmental enrichment induces not only increased neurogenesis, but also a significant increase in the number of hippocampal microglia (probably due to increased microglial proliferation) (Ziv et al., 2006). The microglia in the enriched animals assumed a neuroprotective phenotype, expressing MHC class II and the neurotrophic factor insulin growth factor (IGF)-1 (which is known to promote neurogenesis). The influence of microglia on neurogenesis may be related to their interactions with T cells, since in transgenic mice with excess CNS-specific T cells the increased neurogenesis was attenuated by chronic treatment with the microglial inhibitor minocycline (Ziv et al., 2006). As mentioned above, *in vitro* data on T cell–microglial interactions supports this notion, demonstrating that microglia activated by the T cells-derived cytokine interferon (IFN)-γ induce neuronal differentiation (Butovsky et al., 2006). Consistently, transgenic mice with brain-specific expression of IFN-γ display elevated levels of neurogenesis (Baron et al., 2008). In contrast with these findings, a recent study demonstrated that exposure of mice to spontaneous activity in a running wheel resulted in dramatic neurogenesis, with no signs of microglial proliferation or activation, and no indication of T cell–microglial interactions (i.e., no MHC class II expression or presence of T cells in the hippocampus) (Olah et al., 2009).

Microglia were also shown to play a neurogenesis supportive role in adrenalectomized rodents. This surgical manipulation, which eliminates endogenous glucocorticoids, resulted in tripling neurogenesis rate along with an 8-fold increase in the number of activated microglia. Interestingly, the number of activated (but not resting) microglia highly correlated with the number of BrdU-labeled new neurons. The activated microglia seemed to exert their beneficial effect via expression of the anti-inflammatory/neuroprotective cytokine transforming growth factor-beta (TGF-β1), which was documented to be essential for adrenalectomy-induced increased neurogenesis (Battista et al., 2006). Consistently with the latter, TGF-β over-expression (induced by injection of an adenoviral vector expressing this anti-inflammatory cytokine) increased neurogenesis in the subventricular zone (Mathieu et al., 2010b).

Additional evidence for a role of microglia in neurogenesis is derived from a study reporting that under quiescent conditions microglia in the SVZ are in an intermediate state of constitutive activation compared with non-neurogenic cortical areas. Moreover, the basal level of proliferation of SVZ microglia is much higher than in surrounding forebrain areas. Although these findings support an association between microglial activation and neurogenesis, it should be noted that no such relationship was found in the other neurogenic area of the brain (the SGZ) (Goings et al., 2006). Further evidence for a role of microglia in neurogenesis was provided using a culture system of the SVZ, in which neuropoietic cells continue to proliferate and differentiate, but progressively lose this ability with continued culture. In this model, neurogenesis can be rescued by co-culture with microglia or microglia-derived conditioned medium, indicating that microglia provide secreted factor(s) essential for neurogenesis (Walton et al., 2006). Further work with adult precursor cell cultures demonstrated that activated microglia cells release soluble factors that direct the differentiation of neural precursor cells toward a neuronal phenotype (Aarum et al., 2003).

A role for innate immunity-like process in neurogenesis was also suggested by the finding that neural precursor cells (NPCs) express toll-like receptor (TLR) 2 (which in the brain is usually associated with microglia and other innate immune cells). Moreover, signaling via this receptor was found to positively regulate NPCs differentiation (Rolls et al., 2007).

*1.3.3. Pro-inflammatory cytokines and prostaglandins*

Although most studies in this area implicated pro-inflammatory cytokines in suppression of neurogenesis, there is evidence that at least under some conditions TNFα may have a pro-neurogenic role. Specifically, exposure of neural stem cells (NSCs) to TNFα produced a dose–response related increase in proliferation, with no effect on NSCs differentiation. The signaling cascade involved in this effect was found to depend on TNFα-induced IKK-α/β-complex, which activates the NFκB pathway, which in turn activates the TGFβ activated kinase-1 (TAK-1) signaling cascade (Widera et al., 2006). These findings corroborate a previous study, demonstrating that i.p. injection of TNFα increases the proliferation of neural progenitors in the subventricular zone (Wu et al., 2000).

The finding that COX-2 inhibitors are potent suppressors of neurogenesis (producing 40–90% reductions in the number of proliferating neurons in the hippocampus and SVZ) strongly implicates prostaglandins in this process. Because COX-2 is not expressed by the proliferating progenitors *in vivo*, and COX-2 inhibitors do not affect the growth rate of cultured progenitor cells, it may be suggested that the effect of these drugs is indirect. Since COX-2 is highly expressed by resting microglia that closely associate with the proliferating precursor cells, it is likely that COX-2 inhibitors produce their effects by acting on these cells (Goncalves et al., 2010).

### 1.4. Possible mechanisms underlying the beneficial effects of immune processes in neurobehavioral plasticity

#### 1.4.1. Neuroendocrine–immune interactions

Emotional arousal or mild stress reactions are an essential component of many types of neurobehavioral plasticity. The formation of long-term memory and neural plasticity depends on a process of consolidation, in which new memories, which in the short term exist in a relatively fragile state, undergo a process of stabilization. During this process, which depends on protein synthesis, memory becomes much less amenable to interference (McGaugh, 2000). Consolidation of memories enables the modulation of memory strength by endogenous processes activated by an experience. Such modulation is particularly relevant for memory associated with emotionally arousing experiences, which are modulated by stress-induced activation of the HPA axis (and the secretion of glucocorticoids), as well as the activation of the SNS in the periphery and activation of monoaminergic neurotransmitter systems in the brain. Specifically, the secretion and actions of glucocorticoids, norepinephrine, dopamine and serotonin can facilitate memory consolidation, and the actions of these compounds on memory storage circuits can induce or strengthen LTP and its molecular substrate (McGaugh, 2000; Schwabe et al., 2010). Interestingly, both LTP and neurogenesis can also be strongly facilitated by monoamines (Bliss et al., 1983; Brezun and Daszuta, 1999). It should be noted, however, that under severe stressful conditions over-activation of the HPA axis and monoaminergic neurotransmission can disrupt memory consolidation (McEwen, 1999; Roozendaal, 2000; Schwabe et al., 2010) (see Section 2.4.2).

In view of the multiple levels of interactions between immune parameters, the HPA axis and monoaminergic neurotransmission, these systems are excellent candidates for mediating the effects of immune processes on memory functioning and neural plasticity. These interactions are bi-directional: on the one hand emotional and stressful conditions along with the resultant HPA axis and monoaminergic stimulation induce activation of immune-like processes, and on the other hand, immune-like processes play an important role in mediating the neuro-hormonal stress responses. Most research on these interactions was conducted in the context of the detrimental role of inflammation in neurobehavioral plasticity. However, interactions between immunity, HPA and SNS activation occur also with respect to mild emotional stimulation/stress, which promotes learning and plasticity. For example, the emotional stimulation that is an integral part of many cognitive processes (such as examination or public speaking in humans or various learning paradigms in rodents) is associated with cytokines (particularly IL-1) production (Brydon et al., 2005; Depino et al., 2004; Goshen et al., 2007; Heinz et al., 2003; Labrousse et al., 2009; Steptoe et al., 2007). On the other hand, cytokine production, particularly in the hippocampus and hypothalamus, is important for mild stress-induced activation of the HPA axis and SNS (Goshen and Yirmiya, 2009) (Fig. 1). As detailed below, under certain conditions these interactions may be beneficial for memory and plasticity.

Many research studies examined the effects of endogenous (stress-induced) or exogenous glucocorticoids (GCs) administration on hippocampal-dependent memory, neural plasticity and neurogenesis, reporting that similarly to the finding on the involvement of cytokines in these parameters the effects of GCs can be either beneficial/facilitatory (particularly at low levels) or detrimental/inhibitory (particularly at high levels) (Conrad et al., 1999; de Kloet et al., 1999; Kim and Diamond, 2002; McEwen and Sapolsky, 1995; Wolf et al., 2009b). The role of GCs in mediating the beneficial effects of immunity was particularly examined by testing the effects of GC receptor blockade on IL-1-induced memory improvement. Rats that were injected i.c.v. with IL-1β displayed improved contextual passive avoidance responses concomitantly with increased corticosterone secretion, however, when IL-1β was co-administered together with the GC antagonist RU486, the beneficial effect on memory was eliminated, as was the increase in corticosterone levels (Song et al., 2003). Consistent with these findings, IL-1rKO mice, which displayed impaired memory performance (Avital et al., 2003), also showed diminished corticosterone secretion in response to mild stressors (Goshen et al., 2003), suggesting that impaired HPA axis activation may mediate the poor memory performance of these mice.

A recent study has provided direct evidence for a dual role of hippocampal glucocorticoids in neurogenesis, by demonstrating that *in vitro* exposure of murine neuronal precursor cells to corticosterone induced either proliferation at low concentrations or cell death at high concentrations. Further *in vivo* experimentation demonstrated that specific peripheral activation of T cells, which produced a small increase in hippocampal corticosterone levels (1- to 2-fold over the physiological amount), increased neurogenesis, whereas treatment with LPS, which induced a 5-fold increase in hippocampal corticosterone levels, produced neurogenesis suppression (Wolf et al., 2009b).

As mentioned above, learning, memory and LTP are importantly modulated by monoamines, including NE, DA and 5-HT (McGaugh, 2000). These neurotransmitters can not only influence neurons, but can also influence the production and secretion of inflammatory mediators by both microglia and astrocytes, via activation of specific monoaminergic receptors expressed by these cells (Pocock and Kettenmann, 2007). The role of NE in glial-induced cytokine secretion is complex: on the one hand acute exposure to NE *in vivo* induces microglial activation and secretion IL-1 (Johnson et al., 2008; Maruta et al., 1997; McNamee et al., 2010a,b). In contrast, endogenous and exogenous adrenergic stimulation during inflammatory conditions, including LPS administration, demyelinating and neurodegenerative diseases, results in decreased secretion of IL-1 and other inflammatory mediators, and in the production of anti-inflammatory cytokines, such as IL-10, IL-1ra, and IL-1 type II receptors (Feinstein et al., 2002; Heneka et al., 2002; McNamee et al., 2010a,b). To date, no studies directly assessed the involvement of monoamines in the beneficial effects of immune activation on memory functioning and neural plasticity.

#### 1.4.2. Neuro–glial interactions

Neural and behavioral plasticity result from specific patterns of neuronal activity. It is now well established that both brain and peripheral immune processes can influence, and be directly influenced by neuronal activity, providing a functional neuro–immune basis for immune modulation of plasticity.

Similarly to the mechanisms underlying the effects of neurons on other neurons, neuro–immune interactions are mediated by the secretion of neurotransmitters and neuromodulators from axon terminals, as well as indirectly by the secretion of hormones from the pituitary and other endocrine glands, and their effects via specific receptors expressed by immune cells. For example, in the periphery immune cells, including T, B, NK cells and monocytes/macrophages, express noradrenergic receptors, whose activation markedly alters the functioning of these cells (Nance and Sanders, 2007). Macrophages/monocytes may also express nicotinic α-7 receptors, allowing modulation of immune functioning by parasympathetic activation (Tracey, 2002). Peripheral immune cells also express receptors for various neuropeptides and hormones that are derived from autonomic nervous system axon terminals or from various endocrine systems (Besedovsky and Del Rey, 2007; Friedman and Irwin, 1997), as well as receptors for the monoamines serotonin and dopamine (although in the periphery these compounds are not secreted by nerve cells). Whereas the involvement of peripheral immune cells in normal neurobehavior-

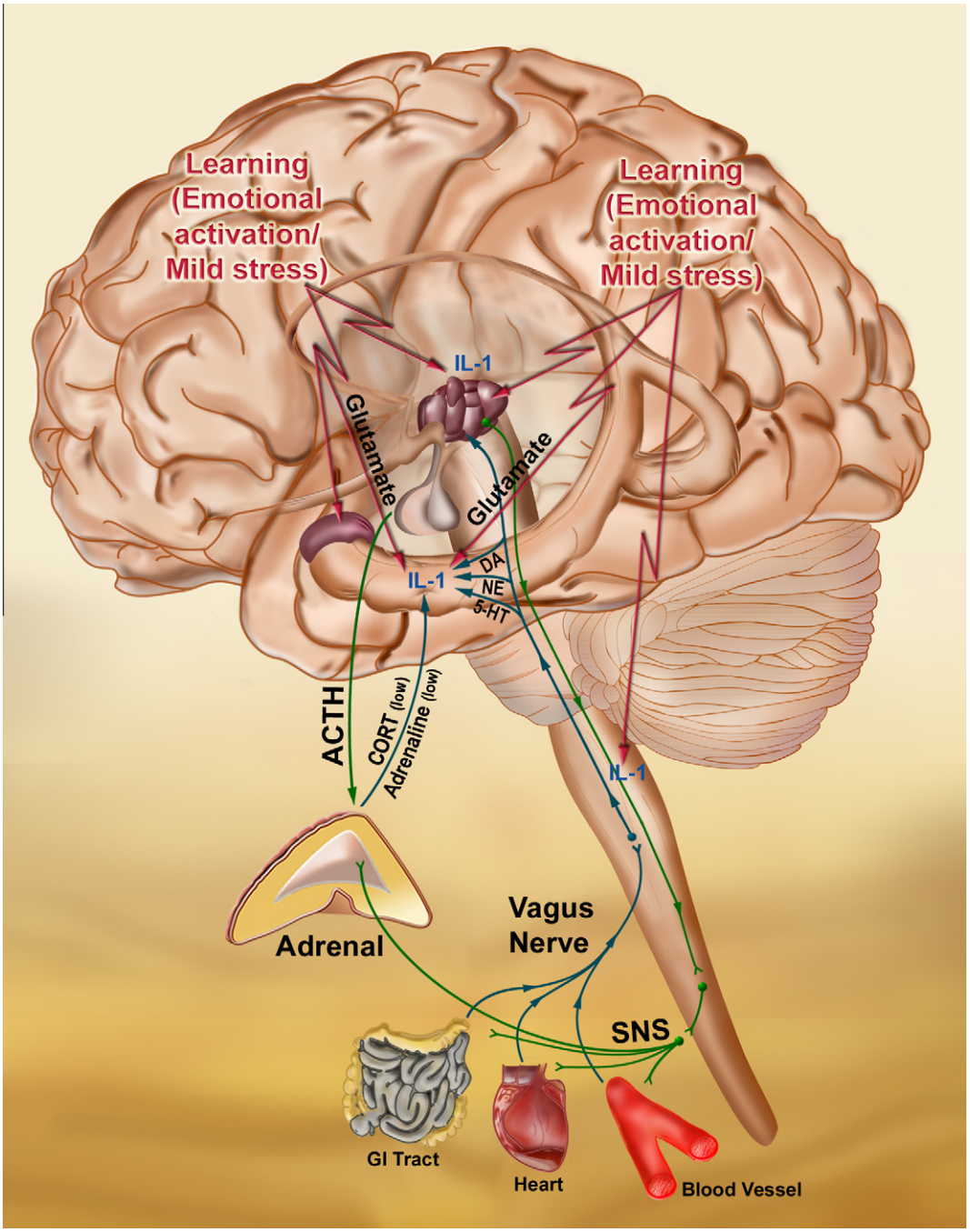


**Fig. 1.** A systemic model of the beneficial role of immune processes in behavioral and neural plasticity. Learning, memory and synaptic plasticity involve neural activation of hippocampal circuits by glutamatergic inputs that originate mainly in multiple cortical areas. Long-term memory consolidation also requires emotional (limbic) activation (particularly of the amygdala and hypothalamus), inducing a mild stressful condition, which in turn results in HPA axis and sympathetic nervous system (SNS) stimulation. The peripheral organs that are the targets of these systems (e.g., the adrenal glad, heart, blood vessels and gastrointestinal (GI) tract), in turn, send afferent inputs to the brain that culminate in stimulation of receptors for glucocorticoids, norepinephrine, dopamine and serotonin on hippocampal cells. These inputs are critical for memory consolidation, neural plasticity and neurogenesis. Furthermore, these inputs induce the production of IL-1, and possibly other cytokines, chemokines and immune mediators in the hippocampus, as well as in other brain areas (such as the hypothalamus and brain stem) that are critically important for neurobehavioral plasticity. Moreover, these cytokines, in turn further activate the HPA axis and SNS, thus participating in a brain-to-body-to-brain reverberating feedback loops.

al plasticity is probably indirect, within the brain direct interactions between astrocytes, microglia, neurons and neural precursor cells are critical for various forms of plasticity. Furthermore, astrocytes, microglia and possibly other brain cells (e.g., endothelial cells and perivascular macrophages) also interact with peripherally-derived immune cells located in various structures surrounding the brain, including the perivascular space, meninges and choroid plexus. These interactions activate myeloid and T cells, which in turn, feedback and send regulatory signals affecting the brain cells (Kipnis et al., 2008; Schwartz and Shechter, 2010). A general scheme of these interactions is presented in Fig. 2, and the hypothesized immune-like roles of astrocytes and microglia in memory and neural plasticity are discussed below.

*1.4.2.1. Astrocytes.* Although astrocytes are not considered as immune cells, they do have some immune-like properties, including

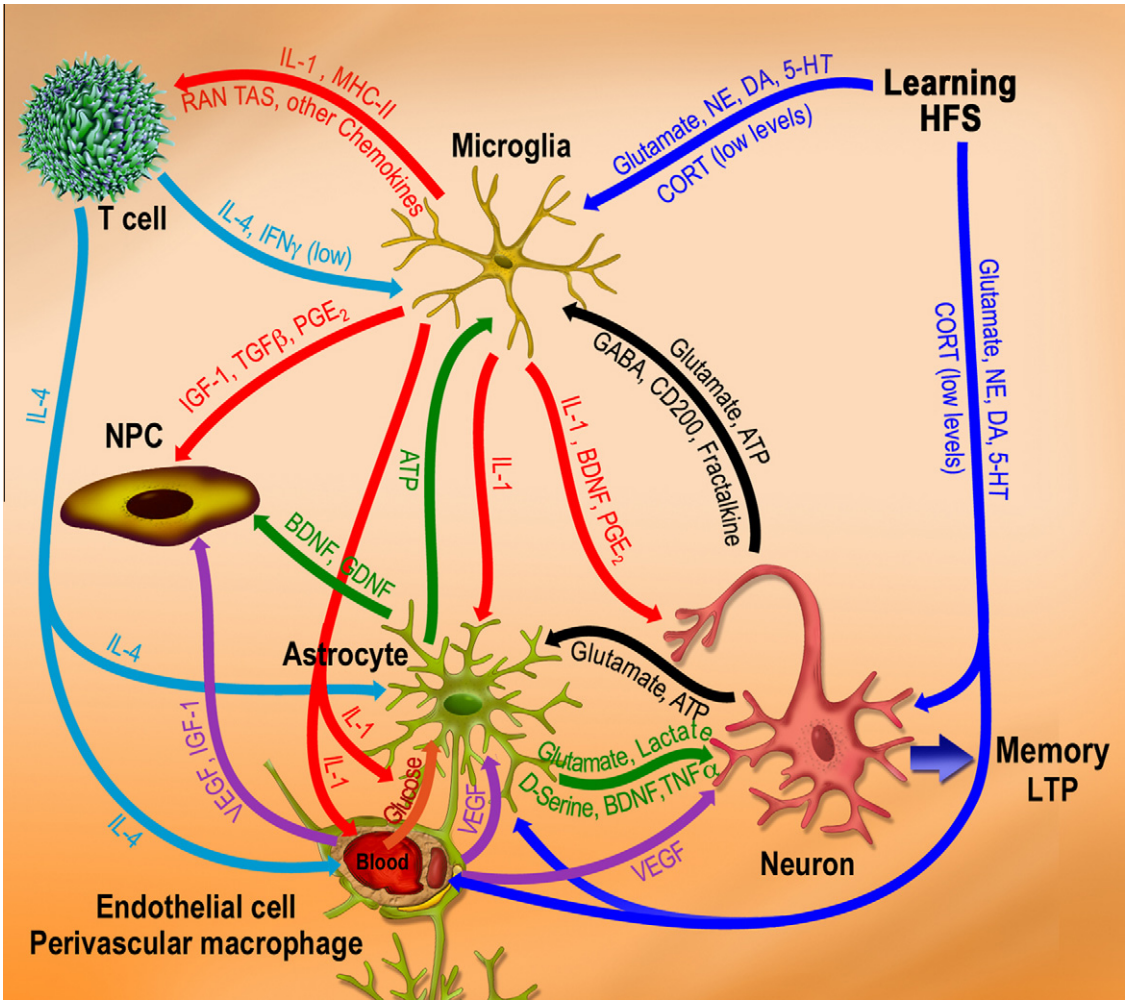


**Fig. 2.** A molecular/cellular model of the beneficial role of immune processes in behavioral and neural plasticity. During learning or high frequency stimulation (HFS) that induces LTP, the external glutamatergic, monoaminergic and adrenocortical input, along with glutamate secreted from neurons within the hippocampus, can activate not only hippocampal neurons, but also hippocampal microglia and astrocytes (blue arrows). Signaling via specific receptors expressed on these glia cells induces the production of various mediators. For example, glutamatergic activation, along with purinergic ATP signaling can direct the production and secretion of IL-1 (as well as other inflammatory mediators) by microglia (red arrows). IL-1 can in turn further activate astrocytes, inducing the secretion of several compounds that are critical for memory formation and synaptic plasticity, such as D-serine, BDNF, TNFα and additional glutamate (green arrows). IL-1 has also been shown to facilitate glucose uptake and the production of lactate by astrocytes, which are important for long-term memory consolidation. Microglia and astrocytes also secrete various compounds that directly influence neuronal functioning and neural precursor cells (NPCs) (which underlie hippocampal neurogenesis), including BDNF, IGF-1, TGFβ, and low levels of TNFα and $PGE_2$. Microglial-derived IL-1 can also directly influence neurons by upregulating NMDA receptor functioning. Importantly, the production of IL-1 and other glial mediators is tightly regulated by neuronal-derived factors, including GABA, CD200 and fractalkine. Microglial expression of IL-1, MHC class II and various chemokines can influence T cells, which play an important role in learning and neurogenesis, possibly via IL-4- and IFNγ-medited interactions with microglia and meningeal myeloid cells (light blue arrows). Finally, IL-1 can activate endothelial cells, which produce various trophic factors, such as VEGF and IGF-1 that are important for memory, neural plasticity and neurogenesis (purple arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

their ability to respond to inflammatory cytokines (particularly to IL-1), to secrete inflammatory cytokines (particularly TNFα and IL-6) (Lee et al., 1993) and to phagocytose cellular processes and debris (Bechmann and Nitsch, 1997). The immune-like nature of astrocytes is particularly notable considering that recent studies indicate that these cells are not merely the supportive cells of the brain, but that they also play an important integral role in neural and synaptic functioning (Halassa and Haydon, 2010; Henneberger et al., 2010; Volterra and Meldolesi, 2005). Specifically, astrocytic processes ensheath most synapses in the brain, and express receptors for several neurotransmitters. Signaling via these receptors evokes elevations in astrocytic Ca2+ concentration, resulting in the regulated secretion of various gliotransmitters, which modulate neuronal excitability and synaptic strength (Halassa and Haydon, 2010; Perea and Araque, 2007). Astrocytes-to-neurons communication also plays a critical role in neurobehavioral plasticity (Bains and Oliet, 2007). For example, female mice in which the transcription nuclear factor-kappa B (NFκB) was inhibited specifically in astrocytes displayed deficits in learning, memory and LTP (Bracchi-Ricard et al., 2008). Moreover, pharmacologic blockade of astrocytic glutamate uptake in rats was also found to impair spatial memory (Bechtholt-Gompf et al., 2010), and motor skill learning was reported to be associated with astrocytic hypertrophy, which was reversed in the absence of continued training (Kleim et al., 2007). In addition, several studies established that astrocytic energy metabolism is involved in memory consolidation and in the influence of noradrenergic mechanisms on hippocampal-dependent memory (Gibbs et al., 2006). These metabolic effects may be related to the findings that IL-1 facilitates glucose uptake and the astrocytic production of lactate (Del Rey et al., 2006; Vega et al., 2002), which is important for long-term memory consolidation (McNay et al., 2000).

A role for astrocytes in LTP was demonstrated in several studies that implicated astrocytic GFAP and S-100β in regulation of LTP (Nishiyama et al., 2002; Tanaka et al., 2002). Furthermore, in both hippocampal cell cultures and slices, the induction of LTP was found to depend on the presence of astrocytes and the secretion of D-serine by these cells, which in turn binds to the glycine-site on neuronal NMDA receptors and enables their critical role in LTP (Henneberger et al., 2010; Yang et al., 2003). Astrocytes also mediate other forms of plasticity, such as homeostatic synaptic scaling following prolonged inhibition of neuronal activity, via secretion of the pro-inflammatory cytokine TNFα (Kaneko et al., 2008; Stellwagen and Malenka, 2006), a known synaptic strength enhancer, which increases the surface expression of AMPA glutamatergic receptors (Beattie et al., 2002).

To test directly the role of astrocytes, and their interaction with immune mechanisms, in neurobehavioral plasticity we recently investigated the involvement of astrocytes in memory and LTP, using IL-1rKO mice as a model of impaired learning and synaptic plasticity. NPCs derived from either WT or IL-1rKO neonatal mice, were labeled with BrdU and transplanted into the hippocampus of either IL-1rKO or WT adult host mice. Transplanted NPCs showed long-term survival and differentiated into astrocytes (expressing GFAP and S100β), but not to neurons. Moreover, several weeks post-transplantation IL-1rKO mice transplanted with IL-1rKO cells or sham operated displayed severe memory disturbances and a marked impairment in LTP, however, IL-1rKO mice transplanted with WT NPCs (expressing IL-1R1) displayed a complete rescue of the impaired memory functioning, as well as partial restoration of LTP (Ben Menachem-Zidon et al., in press). These findings not only indicate that astrocytes play a critical role in memory functioning and LTP, but they specifically implicate astrocytic IL-1 signaling in these processes.

*1.4.2.2. Microglia.* Within the brain, the prominent representative of the immune system is the microglia cell. These resident, macrophage-like cells, which comprise about 15% of brain cells, were shown to play a critical role in developmental neuronal death in the hippocampus (Wakselman et al., 2008), as well as in the clearance of apoptotic neurons (Takahashi et al., 2005). Moreover, "resting" microglial processes were found to be highly motile (Nimmerjahn et al., 2005), and to continuously and dynamically monitor and respond to the functional status of synapses (Wake et al., 2009).

In the normal, quiescent brain, microglia are controlled by both intrinsic and extrinsic systems. Their functioning is modulated by neuronal activity, via neurotransmitter receptors, particularly glutamate, as well as specific regulatory molecules, such as fractalkine and CD200 (Biber et al., 2007; Hung et al., 2010). They are also modulated by astrocytes, e.g., via the secretion of ATP and its signaling via P2X receptors, particularly the p2X7 receptors, whose activation together with glutamatergic inputs is essential for the secretion of some cytokines, such as IL-1 (Ferrari et al., 2006). Microglia can also directly influence neuronal activity. For example, microglial-derived IL-1β can facilitate NMDA receptor activation in neurons via ceramide-src pathway, as detailed below (Viviani et al., 2003; Yang et al., 2005). Microglial-derived IL-1 can also activate endothelial cells, which produce various trophic factors, such as VEGF and IGF-1 that are important for memory, neural plasticity and neurogenesis (Anderson et al., 2002; Cao et al., 2004).

Despite recent evidence for neural–microglial interactions, and the findings that microglia secrete various plasticity related compounds (e.g., glutamate, BDNF and other neurotrophins, as well as inflammatory cytokines such as TNFα and IL-1), there is minimal evidence for a direct role for microglia in learning, memory and LTP. The only exception is recent work demonstrating an involvement of microglia in the LTP of C-fiber-evoked field potentials in spinal dorsal horn. Specifically, HFS-induced LTP was converted to LTD when rats were pre-treated with microglial inhibitors, such as minocycline (Zhong et al., 2010). Moreover, spinal LTP was found to depend on the activation of microglial Src-family kinases (SFKs), evidenced by the findings that phosphorylated SFK was restricted to microglia and was up-regulated by HFS. Moreover, SFKs inhibitors also converted LTP to LTD. Microglial-derived TNFα seemed to play a role in spinal LTP, since the inhibitory effects of minocycline on spinal LTP were reversed by spinal application of TNFα, and HFS failed to induce LTP in TNF receptor-1 knockout mice or in rats pre-treated with TNFα neutralization antibody (Zhong et al., 2010). HFS-induced spinal LTP was also found to depend of the activation of microglial P2X7 receptors (Chu et al., 2010), which are critical for the production and secretion of IL-1. Indeed, blockade of P2X7 receptors by various methods prevented the induction of spinal LTP, as well as the production of IL-1, and administration of IL-1ra also prevented this type of LTP (Chu et al., 2010). Microglia were also implicated in the induction of LTP of C-fiber-evoked field potentials in the spinal dorsal horn by exposure to ATP. LTP in this paradigm was found to be critically dependent on the activation of P2X4 receptors, which are exclusively expressed by microglia. Moreover, following LTP induction microglial expression of these receptors was upregulated and they signaled via the p38 mitogen-activated protein (MAP) kinase (Gong et al., 2009).

These findings are not only important for explaining injury-associated sensitization in pain pathways that can contribute to chronic neuropathic pain, but they may also directly demonstrate the importance of microglia for neural plasticity in general.

### *1.4.3. Immune-induced alterations in plasticity-related molecular and cellular processes*

Memory and LTP are accompanied by molecular and morphological changes within the participating neurons, including changes in intracellular signaling, expression of immediate-early and then structural genes, changes in receptor presentation and spine size modification. Some of these plasticity-related processes were shown to be influenced by immune mechanisms, as detailed below:

*1.4.3.1. The immediate early genes (IEG) activity-regulated cytoskeleton-associated protein (Arc).* Hippocampal-dependent learning induces the expression of Arc, possibly in relation to NMDA receptor activation and secretion of BDNF (another protein essential for memory consolidation, see below). Moreover, Arc levels are correlated with performance in this task (Guzowski et al., 2001). A role for Arc in the beneficial effects of IL-1 on memory has been recently suggested by demonstrating that basal hippocampal Arc expression is lower in IL-1raTG mice (which display poor memory), and the levels of hippocampal Arc protein in these mice are not increased following exposure to novelty, as they do in WT control mice (Spulber et al., 2009). As will be discussed below, chronic high levels of IL-1 produce opposite effects on Arc (i.e., suppression of hippocampal expression), which are associated with suppression of memory (Frank et al., 2010; Hein et al., 2010).

*1.4.3.2. Synaptic proteins.* Synaptic proteins, which may contribute to memory functioning and plasticity, have been suggested to underlie the role of T cell immunity in memory functioning. Specifically, T cell deficient SCID mice transplanted with bone marrow isolated from SCID mice displayed severe memory deficit in the water maze, as well as markedly reduced levels of expression of two presynaptic proteins (Syt10 and Cplx2). In contrast, SCID mice transplanted with WT-derived bone marrow displayed normal

memory functioning and expression of the two proteins (Ron-Harel et al., 2008).

*1.4.3.3. Neurotrophins.* Neurotrophic factors, such as BDNF, IGF-1, NGF, GDNF, and VEGF are essential regulators of various forms of neural and cellular plasticity, not only during development, but also in the adult organism (McAllister et al., 1999). All of these factors can be secreted by several types of immune cells, including T cells, macrophages, mast cells and microglia (Elkabes et al., 1996; Nakajima et al., 2001), particularly after exposure of these cells to various cytokines, including IL-1, IL-6, and TNF-α (Gadient et al., 1990; Schulte-Herbruggen et al., 2005). Once secreted, these neurotrophic factors can serve as mediators of the beneficial effects of immunity on neural and behavioral plasticity.

*1.4.3.3.1. BDNF.* Most research on the relations between immune mechanisms and neurotrophins in general, and with respect to neurobehavioral plasticity in particular, focused on brain derived neurotrophic factor (BDNF). This is understandable given that the production and signaling of BDNF via the TrkB receptor has been implicated in almost every aspect of neural and behavioral plasticity, including hippocampal-dependent memory (Barnes and Thomas, 2008; Heldt et al., 2007), LTP (Lu et al., 2008) and neurogenesis (Li et al., 2008). BDNF and its Trk-B receptors are expressed not only by neurons, but also by astrocytes and microglia. For example, BDNF secreted by activated microglia can influence neuronal functioning (e.g., produce neuroprotective effects (Batchelor et al., 1999)), but it can also act in an autocrine manner to promote proliferation and survival of microglia (Elkabes et al., 1996; Zhang et al., 2003). BDNF, acting via Trk-B receptors on microglia can also induce sustained elevation of intracellular Ca2+ elevation in these cells (which in turn can have anti-inflammatory effects) (Mizoguchi et al., 2009).

Several lines of evidence suggest that enhanced BDNF signaling underlies the beneficial influence of immune processes on learning, memory, LTP and neurogenesis: (1) Transgenic mice with excess of T cells directed towards a brain self antigen, which exhibit enhanced learning, memory and hippocampal neurogenesis, exhibit elevated levels of hippocampal BDNF expression (Ziv et al., 2006). (2) Cop-1 vaccination, which abolishes the learning deficits induced by neurotransmitter imbalance via boosting T cell activity, was found to induce the production of BDNF by T cells. This response was even greater when the Cop-1 reactive T cells encountered the CNS-related self-antigen myelin basic protein, but not the non-CNS-related ovalbumin, further suggesting the involvement of BDNF in the beneficial effect of immune stimulation on learning and memory (Kipnis et al., 2004). (3) The secretion of BDNF by cultured astrocytes is markedly enhanced by IL-4 (which seems to be essential for the beneficial effects of T cells on learning and memory) (Derecki et al., 2010). Moreover, following water maze training, mice exhibit increased expression of BDNF, whereas IL-4 deficient mice, which display impaired performance in this task, do not show such an increase (Derecki et al., 2010). (4) Systemic depletion of CD4-positive T lymphocytes, which led to significantly reduced hippocampal neurogenesis and impaired reversal learning in the Morris water maze, also decreased BDNF expression in the brain (Wolf et al., 2009a). (5) Memory-impaired mice with transgenic expression of IL-1ra exhibit lower levels of hippocampal BDNF. Moreover, whereas in WT mice learning of a novel environment significantly increased hippocampal BDNF levels as well as ERK1/2 activation (which underlies BDNF's effects on memory consolidation) no such increases were shown in IL-1raTG mice (Spulber et al., 2009). (6) The ibuprofen-induced inhibition of prostaglandin synthesis, which disturbs learning, memory and LTP, is also accompanied by diminished production of $PGE_2$ and BDNF following spatial learning and LTP. Moreover, elevation of BDNF levels by prior exercise in a running wheel increased endogenous BDNF levels sufficiently to reverse the detrimental effect of ibuprofen on spatial learning and LTP, and restored a parallel increase in LTP and learning-related BDNF and $PGE_2$ (Shaw et al., 2003).

*1.4.3.3.2. Insulin growth factor (IGF)-1.* IGF-1 was shown to be involved in memory, plasticity and neurogenic processes, especially in the aging brain (Maher et al., 2006; Sonntag et al., 2005). For example, IGF-1 deficiency results in both memory and LTP impairments (Trejo et al., 2007). A role for IGF-1 in the beneficial cognitive effects of T cells was suggested by the findings that in addition to their deficit in BDNF, SCID mice also exhibit reduced expression of the *igf-1* gene, concomitantly with disturbances in memory functioning and neurogenesis. Transplantation of WT bone marrow rescued the impairment in IGF-1 expression and also restored neurocognitive functioning (Ron-Harel et al., 2008).

*1.4.3.4. Glutamatergic neurotransmission.* Changes in glutamatergic neurotransmission may also mediate the beneficial effects of IL-1 signaling on memory and LTP, as suggested by the findings that: (1) microglial-derived IL-1 can alter neuronal functioning by inducing Src family of kinases-mediated tyrosine phosphorylation of *N*-methyl-D-aspartate (NMDA) receptor NR2B subunit in hippocampal neurons (Viviani et al., 2003; Yang et al., 2005). This IL-1-mediated phosphorylation upregulates the function of NMDA receptors, resulting in greater stimulation-induced increases in intracellular Ca2+ in neurons, which is a critical step in the formation of LTP and long-term memory (Viviani et al., 2003). Although this was hypothesized to mediate the neurotoxic effects of IL-1, this pathway may also mediate the beneficial effects of low levels of IL-1 on memory and LTP (Coogan et al., 1999). (2) Memory impaired IL-1raTG mice display lower basal levels of GluR1 and GluR2 expression (Spulber et al., 2009), though no difference in GluR1 levels was observed in IL-1rKO mice (Goshen et al., 2009). These findings suggest that constitutive hippocampal IL-1 production may be important for maintenance of glutamatergic neurotransmission.

*1.4.3.5. Changes in dendritic morphology.* The accumulation of many studies from the last decade suggests that morphological changes in dendritic spines may be related to memory consolidation and storage (Segal, 2005). For example, spatial learning increases the number and density of spines in the DG (O'Malley et al., 2000), as well as the number of mushroom shaped spines in the CA1 region (Hongpaisan and Alkon, 2007). LTP also induces the formation of new spines (e.g., Engert and Bonhoeffer, 1999). Consistently, memory and plasticity deficiencies are accompanied by spine size reduction (von Bohlen und Halbach et al., 2006), whereas memory improvement is accompanied by spine size increase (Zhou et al., 2008).

In a recent study (Goshen et al., 2009), we reported that out of several memory and plasticity-related molecular and morphological parameters that were investigated in the brains of IL-1rKO and WT mice, reduction in spine size was the only parameter that differed between the two strains. This finding suggests that normally IL-1 is involved in regulation of spine size, and therefore reduced spine size in IL-1rKO mice may contribute to their deficits in memory and LTP. Alternatively, IL-1 signaling may be needed to promote learning and LTP-induced increases in spine size. This hypothesis is consistent with the impairments in learning and LTP produced by acute administration of IL-1ra (Goshen et al., 2007; Ross et al., 2003; Schneider et al., 1998; Yirmiya et al., 2002). Interestingly, IL-1rKO mice that were raised in an enriched environment (EE) did not differ in spine size from their WT controls. The marked increase in spine size in enriched IL-1rKO mice, despite the persistent lack of IL-1 signaling in these mice, suggests that mechanisms other than IL-1 signaling are also responsible for

spine size regulation, and that EE activates mechanisms that bypass the need for IL-1 in controlling spine size.

It should be noted that the reported effect of IL-1 signaling deficiency on spine size, as well as some of the behavioral and physiological data, was obtained using genetically manipulated mice. Because in these animals the modified signaling is present throughout their life span, from conception to maturity, it may influence memory and plasticity either by affecting brain development in a way that will alter its functioning in adulthood, and/or by directly influencing ongoing memory and plasticity processes in the adult brain at the time of testing. Thus, the effects of IL-1 on spine size may also be exerted during pre- or peri-natal development. Indeed, we have shown that exposure to IL-1ra in utero can produce memory deficits similarly to those observed in IL-1rKO mice (Goshen et al., 2007).

## 2. The role of the immune system in learning, memory, neural plasticity and neurogenesis under inflammatory conditions

### 2.1. Detrimental effects of immune activation on learning and memory

#### 2.1.1. Studies in experimental animals

Exposure to pathogens that stimulate the immune system results in altered memory performance, as part of the general sickness behavior syndrome. In particular, viral, bacterial, and parasitic infections, as well as exposure to viral coat proteins or bacterial endotoxin, has been shown to produce impaired memory functioning in rodents, evidenced using various paradigms for assessment of different forms and phases of learning and memory, including the water maze, active and passive avoidance, and fear conditioning tests (e.g., Braithwaite et al., 1998; Cunningham et al., 2009; Gibertini et al., 1995a,b; Kamitani et al., 2003; Lee et al., 2000; Li et al., 2004; Murray et al., 1992; Pugh et al., 2000, 1998; Shaw et al., 2001, 2003; Sparkman et al., 2005; Thomson and Sutherland, 2005). It should be noted that the influence of inflammatory challenges on learning and memory may be confounded by general sickness behavior symptoms exhibited by the subjects, including reduced locomotor speed and elevated stress responses, and therefore the results of such studies should be interpreted cautiously (Cunningham and Sanderson, 2008).

As will be discussed below, inflammatory mediators can markedly impair learning and memory functioning. Furthermore, cytokines and prostaglandins do not only mediate the detrimental effect of immune stimulation during infectious diseases, but they are also directly involved in the memory disturbances that accompany exposure to stressful conditions as well as the aging process.

*2.1.1.1. Effects of inflammatory cytokines.* Because the immune response to medical conditions and the sickness behavior that accompanies them are mediated by pro-inflammatory cytokines, many research groups sought to directly assess the involvement of pro-inflammatory cytokines in memory processes. The data collected in these studies, specifically regarding the cytokines IL-1, IL-6, and TNFα, will be presented in this section.

*2.1.1.1.1. IL-1. (i) Effects of IL-1 administration on learning and memory:* The detrimental effect of IL-1 on memory functioning was first demonstrated by showing that i.c.v. administration of IL-1β 1 h before the beginning of spatial water maze training caused a transient memory impairment in the first trial of the following day. When IL-1β was injected immediately before training, no effect was found, suggesting that IL-1β does not affect the acquisition of spatial memory, but rather the retention of this learning and that the processes triggered by IL-1β require some time to exert their influence on memory (Oitzl et al., 1993). Subsequent studies confirmed this finding and showed that peripheral administration of IL-1β also impaired spatial learning (Gibertini et al., 1995a; Song and Horrobin, 2004). Importantly, in the water maze paradigm IL-1β was found to impair spatial memory, but not non-spatial memory (Gibertini, 1996; Song and Horrobin, 2004). IL-1β-injected mice were also found to be less flexible in adapting to a change in the position of the hidden platform (Gibertini, 1996). Furthermore, the memory impairment caused by IL-1β was restricted to learning under a relatively low motivation condition (i.e., when the water in the maze were kept at 23 °C), whereas under a condition of increased motivation to escape (induced by reducing the water temperature to 15 °C), IL-1β administration had no effect (Gibertini, 1998).

In contrast with these findings, other studies, using somewhat different regimens of IL-1 administration and testing procedures, found no effect of IL-1 on spatial memory. Specifically, in one study, daily administration of IL-1β, commencing a week before as well as during training in the water maze, had no effect on spatial learning (Lacosta et al., 1999). In another study, mice that were trained in the water maze using a spaced-learning protocol displayed normal latency to reach the platform following IL-1 injection, despite the fact that the IL-1β-injected mice used a different strategy to find the platform (Gibertini, 1998). Taken together, the findings presented above suggest that IL-1 interferes specifically with spatial learning in the water maze, which depends on normal hippocampal functioning. However, these effects are not demonstrated under all conditions and depend on various experimental parameters.

The involvement of IL-1 in memory processes was also examined using the fear-conditioning paradigm. Intracerebral administration of IL-1β (either into the ventricles or directly into the dorsal hippocampus), immediately following the learning experience, impaired contextual (hippocampal-dependent) but not auditory-cued (hippocampal-independent) fear conditioning in rats (Barrientos et al., 2004; Gonzalez et al., 2009; Pugh et al., 1999). A recent study demonstrated that even protracted administration of IL-1β (up to 12 h after the conditioning session) can impair long-term memory, and these detrimental effects could be blocked by the anti-inflammatory neuropeptide α-melanocortin, acting through activation of MC4 receptors (Gonzalez et al., 2009). The specificity of the detrimental effects of IL-1β to hippocampal-dependent memory was verified using a different version of the contextual fear-conditioning paradigm. In that version, rats are pre-exposed to the context one day before the conditioning session, in which they receives a shock immediately when re-entering this context, followed by prompt removal from that context. The pre-exposure provides an opportunity to generate a mental representation of the context, and without it conditioning will not take place when an immediate shock is applied. This separation between the hippocampal-dependent memory of the context and the conditioning process itself enabled the researchers to pinpoint the exact component of the learning process in which IL-1 is involved. Indeed, intrahippocampal IL-1β administration, immediately after the pre-exposure to the context, impaired the contextual fear conditioning to a much greater extent than a similar administration at the time of context-shock association (24 h after the pre-exposure). Furthermore, when IL-1β was injected at the time of testing (48 h after pre-exposure to the context), no effect on the fear response was observed (Barrientos et al., 2002). These data suggest that the detrimental effect of IL-1 on contextual fear conditioning is caused by interference with the formation of a mental representation of the context by the hippocampus, rather than with the association of this representation with the shock.

Another learning and memory task in which IL-1 is critically involved is spatial active avoidance, in which mice learn to avoid an electrical shock by entering a specific arm of a T-maze. Specifically, mice administered with either human IL-1α or IL-1β required more

trials in order to learn to perform the avoidance response than control mice (Banks et al., 2001). Much lower doses were needed to achieve this detrimental effect when human IL-1α and IL-1β were administered bilaterally into the posterior septum, connecting the hippocampus and the midbrain (Banks et al., 2001, 2002).

IL-1β was also found to impair performance in the three-panel runway, the radial arm maze, and the autoshaping paradigms, which also depend on intact hippocampal functioning. Specifically, in the three-panel runway task, which measures working memory, intrahippocampal administration of IL-1β produced memory impairments, reflected by increased number of errors (Matsumoto et al., 2004, 2001). In the win-shift working memory version of the radial arm maze, IL-1β also significantly increased the number of errors (Song et al., 2004b; Taepavarapruk and Song, 2010). Finally, in the autoshaping procedure, in which rats learn to press a lever to hasten the appearance of a delayed food reward, IL-1β delayed the acquisition of autoshaping in a dose-repose manner (Aubert et al., 1995).

*(ii) Effects of transgenic over-expression of IL-1 on memory functioning:* The studies described above demonstrate the detrimental effects of acute IL-1 administration on learning and memory. To explore the effects of chronic exposure to IL-1, a recent study examined the effects of chronic transgenic over-expression of IL-1β within the hippocampus. Sustained (14 days) elevation of hippocampal IL-1β levels, which resulted in neuroinflammation (reflected by microgliosis and increased production of various inflammatory mediators) produced marked impairments in spatial memory tested with the water maze paradigm, as well as impaired long-term contextual fear memory (Hein et al., 2010; Moore et al., 2009). In both studies, the effects were restricted to hippocampal-dependent memory. Further experimentation and analysis demonstrated that the levels of hippocampal IL-1α were significantly correlated with the memory deficit (Moore et al., 2009) and that IL-1-induced sustained neuroinflammation also reduced basal and conditioning-induced levels of the plasticity-related gene Arc (Hein et al., 2010).

*(iii) Mediation of inflammation-induced memory disturbances by IL-1:* Several studies examined the role of IL-1 in memory impairments caused by various inflammatory agents. Inoculation with Legionella pneumophila bacterium, which markedly increased IL-1β levels in mice, 24 h before training in the spatial water maze task significantly impaired learning. However, when mice were injected with anti-IL-1β antibodies 2 h before training, this bacterial infection had no effect on spatial memory (Gibertini et al., 1995a,b). Peripheral administration of LPS, which is considered an established model of infection, was found to impair learning and memory in various paradigms. Specifically, administration of a dose of LPS that had been shown to elevate hippocampal IL-1 levels in the hippocampus (Nguyen et al., 1998), impaired contextual, but not auditory-cued fear conditioning. Moreover, when the LPS injection was immediately followed by IL-1ra administration, the detrimental effect on memory was abolished (Pugh et al., 1998). Similarly to these findings, i.c.v. injection of the HIV coat protein gp-120 was found to increase IL-1β level in the hippocampus and impair contextual, but not auditory-cued, fear conditioning. Moreover, i.c.v. administration of IL-1ra, immediately following the HIV gp-120 injection, blocked its detrimental effect on memory, implicating the elevated brain IL-1 levels in AIDS-associated memory disturbances (Pugh et al., 2000). IL-1 was also found to mediate memory impairments during chronic brain inflammation, induced by a delayed-type hypersensitivity (DTH) response to the bacterium Bacillus Calmette–Guerin in the hippocampus. The hippocampal DTH response resulted in elevated levels of IL-1β, concomitantly with memory impairment, reflected by decreased exploration of a novel, unrecognized arm in the Y-maze paradigm. Chronic administration of IL-1ra for 10 days before the memory test completely abrogated the memory disturbance induced by hippocampal DHT (Palin et al., 2004).

Brain injury produces neuroinflammation and elevated levels of brain IL-1, concomitantly with disturbances in learning and memory (Allan et al., 2005). Moreover, blockade of IL-1 signaling, using either IL-1ra or IL-1β neutralizing antibody, attenuated spatial learning and memory deficits in the water maze, although it had no effect on injury-induced motor dysfunction (Clausen et al., 2009; Sanderson et al., 1999). It should be noted, though, that in these studies IL-1ra also attenuated brain-injury-induced lesion volume so the effects of IL-1 on learning and memory following injury may be secondary to its effects on neuronal loss.

Perinatal infection or exposure to LPS was also shown to affect learning and memory functioning, at least partly via alterations in IL-1 signaling. Specifically, peripheral infection with *Escherichia coli* on postnatal day 4 in rats resulted in markedly impaired learning and memory due to an inflammatory (LPS) challenge in adulthood (Bilbo et al., 2008, 2005a,b, 2007). Perinatal LPS exposure also disrupted learning, memory and neural plasticity in adult rats (Fan et al., 2010; Harre et al., 2008; Kohman et al., 2008; Lante et al., 2008). The neonatal inflammatory treatments were associated with an exaggerated microglial activation and hippocampal IL-1 production in adulthood (Bilbo et al., 2005a, 2007) (but see (Bilbo et al., 2005b; Kohman et al., 2008)). Moreover, caspase-1 inhibition (which abrogates the production of IL-1) completely prevented the LPS-induced memory impairment, implicating IL-1 in the effects of neonatal infection and inflammation on the cognitive alterations in adulthood (Bilbo et al., 2005a).

*(iv) Mediation of stress-induced memory disturbances by IL-1:* Exposure to acute and chronic stressors was found to induce IL-1β (and IL-1ra) gene expression and protein levels, both in the periphery and in several memory- and plasticity-related brain regions (Goshen and Yirmiya, 2009). A role for IL-1 in mediating the detrimental effects of stress on memory functioning was first demonstrated using the learned helplessness paradigm, in which rats subjected to a series of inescapable shocks learn that nothing they do has any effect on the shocks, and therefore when tested 24 h later in the active avoidance task (in which they do have a possibility to avoid or escape the shocks) they display impaired performance. I.c.v. administration of IL-1ra before inescapable shock administration blocked the learned helplessness (Maier and Watkins, 1995). In a subsequent study, the same research group discovered that rats exposed to 5 h of social isolation displayed a significant increase in hippocampal IL-1β levels, along with impaired contextual, but not auditory-cued fear conditioning memory. Furthermore, i.c.v. administration of IL-1ra before social isolation blocked the effect of this stressor on contextual memory (Barrientos et al., 2003; Pugh et al., 1999).

We have recently found that chronic isolation also results in elevation of hippocampal IL-1β levels, concomitantly with impaired hippocampal-dependent memory functioning in the spatial version of the water maze and the contextual fear conditioning paradigms. Furthermore, intrahippocampal transplantation of NPCs, obtained from neonatal mice with transgenic over-expression of IL-1ra (IL-1raTG) under the GFAP promoter (which chronically elevated hippocampal IL-1ra levels), completely rescued the stress-induced memory impairment (Ben Menachem-Zidon et al., 2008).

*(v) Mediation of aging-induced memory disturbances by IL-1:* Ample evidence demonstrates that aging is associated with neuroinflammation and elevated production and secretion of pro-inflammatory cytokines in the brain (Krabbe et al., 2004). The role of aging-associated increase in brain IL-1β levels in the memory impairments displayed by aged mice was examined using chronic administration of a caspase-1 inhibitor. This treatment reduced hippocampal IL-1β levels in aged mice to the levels of young mice

and reversed the impairment in contextual fear conditioning exhibited by the aged mice (Gemma et al., 2005).

To sum up, the data presented in this section clearly demonstrates a detrimental effect of elevated IL-1 levels on memory processes. This negative influence was found in various studies to be specific to memory tasks that depend on normal hippocampal functioning, whereas the performance of hippocampal-independent tasks was spared.

*2.1.1.1.2. IL-6.* As mentioned above (Section 1.1.2.2), IL-6 plays a complex and variable role in learning and memory, and can produce opposite cognitive effects under different conditions or contexts. The effects of IL-6 on learning and memory in experimental animals have been studied by several approaches, including acute administration of IL-6, manipulations that produce chronic elevation of IL-6 levels, and testing the effects of IL-6 blockade, as specified below:

*(i) Effects of acute IL-6 administration on learning and memory:* In the first study examining the role of IL-6 in memory processes rats were injected (i.c.v.) with IL-6, either immediately or 1 h before the beginning of a two-day spatial water maze training. In that study, no effects of IL-6 on memory were found at any time-point, although a similar administration of IL-1β did produce a significant memory impairment (Oitzl et al., 1993). Two subsequent studies, using different testing paradigms, also reported that exogenous IL-6 administration did not influence hippocampal-dependent memory processes. In one study, low doses of IL-6, injected (i.p.) 15 min before passive avoidance acquisition had no effect on performance (Bianchi et al., 1997, 1998). Furthermore, no effects on memory were obtained when IL-6 was injected 24 h before active avoidance training (Brennan et al., 2004).

*(ii) The detrimental role of IL-6 in aging-associated memory disturbances:* It is now well established that aging in associated with increases in IL-6 levels. Such changes were described in the aged murine brain (Ye and Johnson, 1999), in the brain of senescence-accelerated mice (Tha et al., 2000), and in human plasma (Krabbe et al., 2004). Because aging is accompanied by cognitive deterioration, these findings led to the hypothesis that IL-6 may mediate age-related memory impairments (e.g., Godbout and Johnson, 2004). In one project, the age-dependent involvement of IL-6 in memory processes was examined in mice that over-express IL-6 in the brain (IL-6TG mice). Mice were tested at 3, 6, and 12 months of age, using the active avoidance paradigm. At 3 months of age, homozygous IL-6TG mice demonstrated impaired learning, whereas heterozygous IL-6TG mice were able to learn the avoidance task as well as control mice. At the age of 6 months, the same mice were re-tested, and once again homozygous IL-6TG mice demonstrated impaired learning, which worsened compared to their performance 3 months earlier. However, at that age, heterozygous IL-6TG mice also exhibited impaired memory, intermediate to that of the control and homozygous IL-6TG mice. By 12 months of age, the performance of both homozygous and heterozygous IL-6TG mice had declined further and became indistinguishable (Heyser et al., 1997). Although the effects of IL-6 overproduction support a detrimental role for IL-6 in learning and memory, these findings should be interpreted in the context of other effects of IL-6 overproduction, particularly neurodegeneration and gliosis.

*(iii) Effects of IL-6 blockade on learning and memory:* The role of impaired IL-6 signaling in learning and memory was tested in IL-6 knockout mice (IL-6KO), using different memory tests. In the passive avoidance task, the performance of 4-month-old IL-6KO mice was similar to that of controls; however, the IL-6KO mice were less susceptible to scopolamine-induced amnesia in this task. Furthermore, when IL-6KO mice were tested in a more complex spatial task – the radial arm maze, their performance was found to be better than age-matched WT controls (Braida et al., 2004). Acute blockade of IL-6 signaling was also found to enhance memory formation. Specifically, i.c.v. administration of neutralizing anti-IL-6 antibodies, 90 min after the acquisition of a forced alternation task, resulted in enhanced retention of this hippocampal-dependent spatial memory 24 h later (Balschun et al., 2004). Together, the findings of improved memory functioning following chronic and acute blockade of IL-6 signaling, suggest that IL-6 may have a physiological role in the inhibition of memory formation.

To sum up, on the one hand IL-6 is associated with detrimental effects on memory, reflected by the association between age dependent increases in IL-6 and memory loss as well as the findings that impaired IL-6 signaling is associated with memory improvement. On the other, acute administration of IL-6 does not produce any effect on memory, and in some conditions (Section 1.1.2.2 above) elevated levels of IL-6 were associated with protection from memory loss in several medical conditions. These findings are consistent with the fact that IL-6 can act both as an inflammatory and as an anti-inflammatory cytokine (Jones et al., 2005), and suggest that the role of IL-6 in memory depends on the specific condition or context under which it is elevated, as well as on the magnitude and duration (acute vs. chronic) of the elevation, and the possible priming status of relevant cells.

*2.1.1.1.3. TNFα.* The involvement of TNFα in memory processes has been studied by several research groups, using various models. Most studies reported no involvement of TNFα in memory functioning. However, a few studies demonstrated a detrimental effect of TNFα on memory formation, and one study reported a beneficial role for TNFα (as noted in Section 1.1.2.3). These contradictory results will be presented, along with possible explanations for the discrepancies among them.

The detrimental effect of TNFα on memory was first demonstrated by showing impaired learning in adult mice that over-express TNFα within the CNS (TNFαTG) in the passive avoidance paradigm (Fiore et al., 1996). Consistently, daily i.c.v. administration of TNFα for a week before water maze training was found to impair spatial learning and memory in this paradigm (Bjugstad et al., 1998). A negative effect of TNFα was also reported following intra-hippocampal administration, which resulted in impaired hippocampal-dependent working memory, reflected by an increased number of errors and longer latencies to perform the three-panel runway task (Matsumoto et al., 2002).

In contrast with these findings, several studies reported less consistent effects of excess TNFα signaling on memory functioning. In two related studies, the influence of elevated TNFα levels on memory was studied using two different transgenic strains that over-express TNFα specifically within the CNS: the TG6074 strain, with glial over-expression of the murine TNFα gene, which display inflammatory demyelination and neurological abnormalities, and the TGK3 strain, with neuronal over-expression of the uncleavable mutant human TNFα gene, which display no neurological symptoms. In the water maze paradigm, both of these transgenic strains displayed longer escape latencies compared with their WT controls at the age of 30 days (Aloe et al., 1999b; Fiore et al., 1996). However, compared to controls, these mice also displayed a slower swimming speed, which may affect the latency to reach the platform. Furthermore, the learning deficit was not observed with respect to the path length to reach the platform, which provides a measurement of learning that is not dependent on speed. Moreover, no difference was found in the preference for the quadrant in which the platform was positioned in the probe test, another memory parameter that is not influenced by swimming speed (Aloe et al., 1999b; Fiore et al., 2000). Together, these findings do not support the hypothesis that excessive brain TNF-α affects spatial memory in young mice. The discrepancy between the results of these studies and the report of impaired spatial memory in TNF-αTG6074 mice (Fiore et al., 1996) may be explained by differences in the age of the subjects. Indeed, because aging is accompanied by

cognitive deterioration, and brain TNFα expression is increased with age (Casolini et al., 2002), it can be postulated that TNFα may be involved in aging-related memory loss. Consistently with this hypothesis, impaired spatial memory was observed in adult (60-day-old) mice (Fiore et al., 1996), but not in young (30-day-old) or juvenile mice with TNFα over-expression (Aloe et al., 1999b; Fiore et al., 2000). Thus, the detrimental effect of TNFα transgenic overexpression in the brain on memory processes seems to be age dependent.

Studies on the effects of TNFα signaling deficiency also resulted in variable and even contradictory findings. In one study, TNFαKO mice were found to exhibit enhanced spatial memory in the water maze paradigm compared to WT controls. In contrast, the TNFαKO mice demonstrated performance that was identical to WT controls in the hippocampal-independent, visually guided version of the water maze (Golan et al., 2004). This finding is consistent with a detrimental role for TNFα in memory. However, in several different studies, TNFα deficiency did not seem to result in memory changes. In two of these studies, different lines of TNFαKO exhibited normal performance in the water maze paradigm (Gerber et al., 2004; Scherbel et al., 1999). In another study, testing spatial memory in the water finding task, the performance of TNFαKO mice was also similar their WT controls (Yamada et al., 2000). Nevertheless, TNFαKO mice were less susceptible to the memory impairment caused by brain injury, which was inflicted by controlled cortical impact (Scherbel et al., 1999), suggesting that in WT mice TNFα participates in the processes underlying this damage.

To sum up, the data gathered so far does not provide definite conclusions regarding the role of TNFα in memory processes. However, it can still be suggested that (A) basal levels of TNFα are not required for memory, as TNFα-deficient mice demonstrate no memory impairments, and one paper even reported improved memory in these mice; and (B) the negative influence of TNFα appears to be both dose and age dependent, and is restricted to the performance of tasks that depend on normal hippocampal functioning.

*2.1.1.2. Effects of prostaglandins.* A detrimental role for prostaglandins in learning and memory has been investigated by three approaches (Hein and O'Banion, 2009).

*2.1.1.2.1. Examining the mnemonic effects of direct administration of $PGE_2$ into the brain.* Intrahippocampal administration of $PGE_2$ was found to impair working memory, examined by the three-panel runway apparatus in rats (Matsumoto et al., 2004), and to dose-dependently reduce memory in the contextual fear-conditioning paradigm (Hein et al., 2007).

*2.1.1.2.2. Examining the effects of COX-2 over-expression.* Transgenic over-expression of COX-2, which resulted in marked elevation of brain $PGE_2$ levels, was found to impair spatial memory in the water maze in aged, but not in young mice (it is suggested that developmental compensatory mechanisms are sufficient to counteract the detrimental effects of elevated $PGE_2$ levels in young animals, and that memory deficits occur when these mechanisms are deteriorating during aging) (Andreasson et al., 2001). Consistently, in a genetic mouse model of AD, over-expression of COX-2 resulted in impaired working memory (which could be blocked by treatment with a COX inhibitor), without any effect on AD pathology (Melnikova et al., 2006).

*2.1.1.2.3. Examining the effects of PGs synthesis blockade on memory functioning in various neuroinflammatory models.* Administration of COX inhibitors was found to reverse memory impairments produced by several conditions associated with neuroinflammation (Hein and O'Banion, 2009), including: (i) *Aging:* Chronic administration of either non-selective COX inhibitors or selective COX-2 inhibitors attenuated age-related deficits in learning and memory, as assessed in the radial arm water maze, contextual fear conditioning, passive avoidance, and elevated plus maze tasks. Interestingly, COX inhibition also attenuated age-related neuroinflammation, including the increase in hippocampal IL-1β levels (Casolini et al., 2002; Jain et al., 2002; Mesches et al., 2004). (ii) *Model of Alzheimer's disease:* The effects of COX inhibitors were examined in several models of AD in rodents. COX inhibitors attenuated the memory loss induced by i.c.v. administration of Aβ (Cakala et al., 2007; Joo et al., 2006), as well as the memory deficits displayed by several genetic models of AD in mice (Kotilinek et al., 2008; McKee et al., 2008). (iii) *LPS administration:* The detrimental effects of LPS administration on memory functioning were also reversed by treatment with non-selective COX inhibitors or selective COX-2 inhibitors. Such effects were found when a COX inhibitor was administered before either acute injection of LPS in the periphery (Jain et al., 2002; Shaw et al., 2005) or directly into the hippocampus (Ma and Zhu, 1997). In addition, COX inhibition blocked the effects of chronic (28 days) i.c.v. administration of LPS, which serves as a model for chronic neuroinflammation (Hauss-Wegrzyniak et al., 1999; Jin et al., 2008). (iv) *Traumatic brain-injury (TBI):* The effects of COX inhibition on the memory loss induced by TBI, which results in neuroinflammation and elevated levels of inflammatory mediators such as IL-1 and $PGE_2$, are not consistent. Two studies reported that treatment with a COX-2 inhibitor attenuated spatial memory loss in the water and Barnes mazes (Cernak et al., 2002; Gopez et al., 2005), however another study found no effect of treatment with a COX-inhibitor on TBI-induced memory deficit in the water maze and fear conditioning paradigms (Dash et al., 2000). (v) *Stress:* The memory retention deficit that was induced by sub-chronic immobilization stress in the elevated plus maze was found to be reversed by treatment with either a non-selective COX-inhibitor or a selective COX-2 inhibitor (Dhir et al., 2006). (vi) *IL-1:* The impairments in contextual fear conditioning and in working memory, which were induced by intrahippocampal IL-1β administration, were found to be blocked by co-administration of the non-specific COX inhibitors naproxen and diclofenac, respectively (Hein et al., 2007; Matsumoto et al., 2004).

*2.1.2. Immune activation and memory disturbances in humans*

Immune activation and inflammatory processes accompany most medical conditions in humans, and therefore can potentially mediate the disturbances in memory functioning and neural plasticity associated with these conditions. Because it is difficult to experimentally manipulate immune parameters in humans, most studies in this area relied on examination of the correlation between serum levels of inflammatory cytokines and memory functioning in various conditions associated with inflammation, including infectious, autoimmune, and neurodegenerative diseases, as well as normal aging. In addition, several recent studies used prospective experimental design to assess the effects of administration of immune challenges or cytokines on memory functioning (Arnold et al., 2002; Krabbe et al., 2005; Reichenberg et al., 2001). Another approach has been to study the relationships between polymorphisms in cytokine genes and the risk and severity of neurodegenerative diseases and dementia. However, these studies usually assessed cognitive functioning and dementia in a global sense (i.e., in most of these studies did not utilize specific and sensitive tests for various memory functions), and therefore will not be reviewed here (see (Goshen and Yirmiya, 2007) for a review of this topic).

*2.1.2.1. The role of inflammatory mediators in memory disturbances associated with infectious and autoimmune diseases.* Inflammatory cytokines are elevated in many medical conditions other than neurodegenerative diseases, including acute and chronic infectious diseases, autoimmune diseases such as lupus and multiple sclero-

sis, as well as following stroke, surgery, or trauma. These conditions are also characterized by transient memory decline and in some conditions even by the development of dementia (e.g., Bucks et al., 2008; Capuron et al., 1999; Gonzalez-Scarano and Martin-Garcia, 2005; Hilsabeck et al., 2002; Patanella et al., 2010; Schmidt et al., 2006). The role of specific cytokines in illness-associated memory disturbances was examined in very few studies, with somewhat inconsistent results. For example, an association between higher levels of IL-6 (but not TNFα) and poor cognitive ability was found in MS patients (Patanella et al., 2010). However, in patients with chronic hepatitis C, who are known to display mild cognitive impairments, no correlations were found between pro-inflammatory cytokine levels and memory functioning. Still, in those patients who displayed detectable levels of endogenous IFNα, high levels of plasma IL-6 and TNFα were significantly related to poorer memory (Hilsabeck et al., 2010). In another study examining elderly people with type-2 diabetes, higher levels of IL-6 and TNFα were correlated with pooper performance in several tests of cognitive abilities, but not with poorer memory (Marioni et al., 2010). In other studies, IL-6 was found to be associated with a protective effect. Specifically, patients with systemic lupus erythematosus, but not with rheumatoid arthritis, exhibited a significant impairment in learning of verbal and non-verbal information, and higher levels of IL-6 in the plasma were associated with higher learning scores (reflecting better short-term memory functioning). This relationship was substantial, accounting uniquely (i.e., after adjustment for depression score and somatic symptoms) for 17% of the variance in learning scores (Kozora et al., 2001). We have recently found additional support for a possible protective effect of IL-6 in illness-associated memory disturbance (Shapira-Lichter et al., 2008), demonstrating that in generally healthy volunteers moderate surgery produced impairments in verbal and visual declarative memory, but not in other cognitive parameters (compared with the participants' own baseline, as well as non-surgical controls). Furthermore, the memory impairments were inversely correlated with the elevation in IL-6 following the surgery, suggesting that post-surgery increases in IL-6 levels are associated with protection from surgery-induced memory disturbances (Shapira-Lichter et al., 2008). Together, these findings underscore the complexity of the associations between pro-inflammatory cytokines and memory, which is described in the sections on experimental animals, demonstrating that under specific situations elevated levels of cytokines, particularly IL-6, may be associated with either detrimental or protective effects on memory functioning.

In another set of studies, we adapted a different approach for examining the relationship between cytokines and memory, using a double-blind, crossover study, in which healthy male volunteers completed psychological questionnaires and neuropsychological tests following endotoxin (LPS) administration. In one experiment, 20 volunteers were tested 1, 3, and 9 h after intravenous injection of endotoxin (0.8 ng/kg) or saline in two experimental sessions (Reichenberg et al., 2001). We found that although endotoxin had no effects on physical sickness symptoms, blood pressure, or heart rate, it induced mild fever and markedly increased the circulating levels of IL-6, TNF-α, soluble TNF receptors, IL-1ra, and cortisol. Endotoxin administration produced a global decrease in memory functions, during all testing periods, reflected by decreased immediate recall of story items, reduced delayed story recall, a deficit in immediate and delayed recall of figure items, and decreased performance in Word List Learning. Furthermore, endotoxin-induced impairments in immediate and delayed story recall were significantly and positively correlated with the secretion of IL-6, TNFα, and IL-1ra in the first and second testing periods, but not in the last period. Interestingly, using the same procedure we demonstrated that in contrast with the cytokine-associated deleterious effects of endotoxin on declarative memory, endotoxin administration induced a significant improvement in working memory performance, reflected by an increased score in the Digit Span Backward Test during all testing periods. This improvement was not associated with cytokine secretion (but it did associate with alterations in cholinergic neurotransmission) (Cohen et al., 2003). In another recent study (Krabbe et al., 2005), we also used a double-blind crossover design, in which 12 healthy young males completed neuropsychological tests before as well as 1.5, 6, and 24 h after an intravenous injection of a very low dose of endotoxin (0.2 ng/kg) or saline in two experimental sessions. Endotoxin administration had no effect on body temperature, cortisol levels, blood pressure, or heart rate, but circulating levels of TNF-α, IL-6, TNF receptors, and IL-1ra were markedly elevated. In this model, low-dose endotoxemia did not affect cognitive performance significantly, but declarative memory performance was inversely correlated with endotoxin-induced increases in circulating IL-6 levels (Krabbe et al., 2005).

*2.1.2.2. The role of inflammatory mediators in memory disturbances associated with normal aging.* The role of inflammatory cytokines in memory functioning was mainly examined in the context of normal and pathological aging. Ample evidence indicates that in normal aging the regulatory mechanisms responsible for inflammatory responses are ineffective or damaged, resulting in adverse pathological conditions (Bodles and Barger, 2004; Krabbe et al., 2004). One of the most consistent findings in gerontological surveys of cytokines is an age-dependent increase in IL-6 levels (Ershler et al., 1993). Some studies also reported that plasma levels of TNFα are also increased in elderly populations (e.g., Bruunsgaard et al., 1999). Although the associations between inflammatory cytokines and aging are quite consistent, it is still not certain whether the increase in inflammatory markers results directly from the aging process per se, or whether it is mediated by indirect processes, particularly sub-clinical disorders like chronic infections and atherosclerosis.

Ample evidence indicates that increases in pro-inflammatory cytokines, particularly IL-6, are associated with cognitive impairment in elderly people. Several longitudinal population-based studies showed that elderly subjects who had high levels of blood IL-6 (usually defined as being in the highest third for plasma IL-6) were also more likely to exhibit poorer cognitive functioning, as well as a greater cognitive decline over 2.5- to 7-year follow-ups (Weaver et al., 2002; Wright et al., 2006; Yaffe et al., 2003). Consistently, plasma IL-6 levels were negatively associated with hippocampal grey matter volume (Marsland et al., 2008). In contrast with these findings, two additional longitudinal studies did not find a significant association between IL-6 levels and cognitive decline (Dik et al., 2005; Wilson et al., 2003). One problem with these studies that can explain this inconsistency is that global tests of cognitive functioning were used, which may not have the required sensitivity to reveal disturbances in specific neuropsychological functions such as memory.

Unfortunately, inconsistent results were also obtained when specific memory functions were assessed. In one study, higher levels of IL-6 levels were found to be associated with lower performance on tests assessing auditory recognition and working memory in middle-aged community volunteers (Marsland et al., 2006). In another study, higher IL-6 levels were also associated with poorer sensory memory, assessed by the intentional memory test, but not with incidental short-term memory (Elwan et al., 2003). However, in contrast with these findings, neither immediate nor delayed recall in the Auditory Verbal Learning Test were found to be associated with IL-6 levels in normal elderly subjects (Dik et al., 2005). Similarly, no associations were found between the plasma levels of IL-6 or IL-1β and short-term memory, assessed

by the word list recall test, although higher levels of IL-8 were significantly associated with poorer performance on this test (Baune et al., 2008). Together, these findings attest to the complexity of the relationships between cytokines and memory functioning in normal subjects, suggesting that many intervening variables should be considered in such studies. For example, the presence of a medical condition can influence the relationship between cytokines and memory functioning in the elderly, as demonstrated by a study in which a significant association was found between TNF-α/IL-10 ratio and memory functioning (including immediate and delayed verbal recall) in subjects above 85 years of age who also had cardiovascular disease. Interestingly, memory functioning did not depend on this inflammatory parameter when cardiovascular disease was absent (van Exel et al., 2003).

*2.1.2.3. The role of inflammatory mediators in memory disturbances associated with neurodegenerative diseases.* Over the last two decades it became evident that inflammatory processes, including the activation of microglia as well as the production and secretion of pro-inflammatory cytokines, play an important role in the pathophysiology of Alzheimer's disease (AD) (Akiyama et al., 2000). From an initial view, implicating neuroinflammation in driving AD pathology, a more complex picture has emerged, depicting inflammatory processes both as potent drivers of disease and as mediators of beneficial responses that reduce disease pathology (Lucin and Wyss-Coray, 2009; Schwartz et al., 2009; Shaftel et al., 2008). Unfortunately, all the studies on the relationships between immune processes and cognitive functioning in AD patients, which are detailed below, utilized global neuropsychological rating scales (either the Mini Mental State Examination or a composite global score from various attention, memory, language, and executive function tests), and therefore these reports do not allow drawing conclusions with respect to specific impairments in memory.

It is now clear that AD is associated with elevated serum and cerebrospinal fluid (CSF) levels of TNF-α, IL-6, and IL-1β (Akiyama et al., 2000; Shaftel et al., 2008). Furthermore, post-mortem brain tissues from patients suffering from AD show increased production of pro-inflammatory cytokines, particularly near the senile plaques (Griffin et al., 1995; Griffin et al., 1989). In Down syndrome individuals, which develop AD in middle age rather than in old age, brain IL-1 and plasma IL-6 are also dramatically elevated already at a young age, before the appearance of dementia (Licastro et al., 2005). Several recent studies prospectively assessed the predictive value of elevated pro-inflammatory cytokines for the risk of developing AD in cognitively intact individuals or for aggravating AD symptoms in patients who were already diagnosed with the disease. Higher plasma levels of the inflammatory marker α1-antichymotrypsin and IL-6 (Engelhart et al., 2004), as well as higher spontaneous production of IL-1 or TNFα by peripheral blood mononuclear cells (Tan et al., 2007) were found to be associated with increased future risk of AD in older individuals. In AD patients, acute or chronic systemic infections and the associated pro-inflammatory cytokine production was found to aggravate the AD symptoms (Perry, 2004). Specifically, in one study AD subjects who had detectable serum levels of IL-1β at baseline had an increased rate of cognitive decline over a 2-month follow-up, compared with those with no detectable levels of IL-1β (Holmes et al., 2003). Similarly, in demented subjects with AD, higher levels of IL-6 were correlated with the severity of the dementia (Kalman et al., 1997). Finally, acute systemic inflammatory events and the associated increase in serum levels of TNFα dramatically increased the rate of cognitive decline in AD patients over a 6-months period. In contrast, subjects who had low levels of serum TNFα throughout the study showed no cognitive decline over the 6-month period (Holmes et al., 2009).

Increased levels of IL-1β (Forlenza et al., 2009) as well as TNFα and COX-2 (Bermejo et al., 2008) were also associated with mild cognitive impairment (MCI), particularly in subjects with the multiple-domain amnestic type MCI. Subjects in this group had high IL-1β levels, similarly to those displayed by AD patients, and significantly greater than those displayed by normal controls or subjects with non-amnestic MCI (Forlenza et al., 2009). This finding is consistent with a recent study showing that high plasma levels of the inflammatory marker CRP are also associated with MCI (Roberts et al., 2009).

These phenomena were mostly taken to suggest that microglial activation and elevated levels of inflammatory cytokines, such as IL-1, contribute to neurodegeneration in AD. However, in animal models of AD, microglia were recently found to promote the clearance of amyloid plaques, (El Khoury et al., 1996; Paresce et al., 1996; Simard et al., 2006). Moreover, it has been shown that regulation of Aβ-activated microglia by IL-4 derived from T helper cells reverses their toxic inflammatory characteristics (Butovsky et al., 2005, 2006). Consistently, pharmacological or genetic inhibition of microglial functioning reduces Aβ clearance and accelerated disease progression (Seabrook et al., 2006; El Khoury et al., 2007). Interestingly, a recent study (Shaftel et al., 2007) surprisingly demonstrated that sustained transgenic IL-1 over-expression in a mouse model of AD led to a reduction in amyloid pathology, mediated by enhancement of microglia-dependent plaque degradation. However, as described above, such sustained transgenic IL-1 overexpression produces marked impairments in hippocampal-dependent memory (Hein et al., 2010; Moore et al., 2009). Thus, it may be argued that IL-1 and neuroinflammation may be beneficial for plaque degradation and phagocytosis (at least in the initial stages of the disease) and detrimental for other psychological and neurological aspects, including memory disturbances and reduced neurogenesis (Shaftel et al., 2007).

### 2.2. Detrimental Effects of immune activation on hippocampal LTP

As mentioned above, although it is not clear whether synaptic plasticity is sufficient for memory formation, many studies showed that inhibited synaptic plasticity accompanies learning and memory impairments (see (Martin et al., 2000) for review). This observation is also true for the effects of immune system activation. Along with the memory impairments described in the previous section, LTP is also inhibited by infection (and its modeling by LPS administration), trauma, neurological diseases, severe or chronic stress and natural aging (Dong and Xiong, 2006; Hauss-Wegrzyniak et al., 2002; Jacobsen et al., 2006; Kim et al., 1996; Li et al., 2004; Lynch, 1998a,b; O'Donnell et al., 2000). Moreover, the effects of these conditions are mediated by cytokines and prostaglandins, as will be described below.

#### 2.2.1. Effects of inflammatory cytokines

*2.2.1.1. IL-1.* Several lines of evidence indicate that IL-1 can impair the induction and maintenance of hippocampal LTP. In the first study on this topic, IL-1β application was found to inhibit LTP in the CA3 region of mouse hippocampal slices (Katsuki et al., 1990). A similar IL-1-induced LTP inhibition was also found in the rat CA1 area (Bellinger et al., 1993) and the DG (Cunningham et al., 1996). These detrimental effects of IL-1 were accomplished by inhibition of both NMDA-mediated and NMDA-independent synaptic potentiation (Coogan and O'Connor, 1997, 1999). In addition, the maintenance of LTP was found to be negatively associated with increased IL-1β levels in the hippocampus (caused by aging, stress, or exogenous application) (Murray and Lynch, 1998).

In addition to its effects on LTP, IL-1 was also reported to affect basal synaptic activity. Specifically, incubation of hippocampal slices with IL-1β decreased basal CA1 synaptic transmission

(Bellinger et al., 1993; Ikegaya et al., 2003). This effect could be demonstrated for 30 min after IL-1 was washed out of the system. This durable effect was dependent on increased GABA levels, as in the presence of the GABA receptor antagonist bicuculin, IL-1 decreased synaptic transmission only when it was present in the experimental system, but not after it was washed out (Ikegaya et al., 2003).

Disruption in the balance of hippocampal IL-1 activity may be associated with the findings of age dependent decrease in LTP (Lynch, 1998a,b; O'Donnell et al., 2000). Specifically, aging is accompanied by an increase in basal hippocampal IL-1β (and IL-18) levels, which is temporally correlated with the LTP impairment (Griffin et al., 2006; Murray and Lynch, 1998; O'Donnell et al., 2000). A role for microglia in this phenomenon is suggested by the finding that treatment with the microglial inhibitor minocycline partially restores LTP in aged rats (Griffin et al., 2006). The detrimental effects on LTP exerted by Amyloid β, which increases in normal aging and particularly in Alzheimer's disease, may be also mediated by IL-1 because IL-1ra administration was found to attenuate the depression of LTP in the CA1 region of the hippocampus *in vivo* following i.c.v. administration of Aβ-peptide (1–40) (Schmid et al., 2009). Interestingly, aging is also associated with a diminished increase in LTP-induced IL-1β gene expression. Specifically, IL-1β expression is increased by 10-fold in young rats during LTP, but only by 2-fold in mid-aged rats (Balschun et al., 2003). Together these findings suggest that deviations in either direction from the fine balance of hippocampal IL-1 levels may lead to LTP maintenance impairments in aging.

To sum up, the data presented above clearly demonstrate a detrimental effect of elevated IL-1 levels on hippocampal LTP. This negative influence was replicated in various studies, both *in vivo* and *in vitro*, using different doses of exogenously applied IL-1β, as well as endogenous IL-1β elevation caused by aging and stress.

*2.2.1.2. IL-6.* Several studies demonstrated that IL-6 can impair hippocampal plasticity. In hippocampal slices prepared from transgenic mice with cerebral over-expression of IL-6, LTP in the DG was markedly reduced, compared with WT controls (Bellinger et al., 1995). Similarly, exposure of hippocampal slices to IL-6 attenuated tetanic stimulation-induced LTP in the CA1 region (Li et al., 1997; Tancredi et al., 2000, 1992). This effect was mediated via the IL-6 receptor, as it was blocked by antibodies against this receptor (Li et al., 1997), and was dose dependent, i.e., at low doses IL-6 seems to be involved mainly in the process of the transformation between short- and long-term plasticity, but at higher concentrations it can interrupt the LTP process itself. In contrast, no study reported a significant effect of IL-6 on basal synaptic transmission, and elevated IL-6 levels (either by transgenic over-expression or by external application) had no effect on paired-pulse responses (Bellinger et al., 1995; Tancredi et al., 2000), indicating that this cytokine is not involved in short-term plasticity.

*2.2.1.3. TNFα.* Although TNFα plays an important beneficial role in two forms of long-term plasticity – synaptic scaling and deprivation-induced cortical plasticity (see Section 1.2.1.3), its role in acute plasticity is detrimental. Whereas normal, physiological levels of TNFα do not seem to be involved in LTP induction or maintenance, several studies demonstrated that exposure to elevated levels of TNFα can result in suppression of LTP. All of these studies were conducted in hippocampal slices, and showed dose-dependent decreases in LTP in either CA1 or DG synapses (Butler et al., 2004; Cunningham et al., 1996; Curran and O'Connor, 2003; Pickering and O'Connor, 2007; Tancredi et al., 1992).

*2.2.2. Effects of prostaglandins*

Although basal levels of $PGE_2$ seem to be required for LTP (Section 1.2.2), elevated levels of PGs may be detrimental for LTP. Specifically, selective inhibition of COX-2 was found to block Aβ-mediated inhibition of LTP (despite a lack of effect on the levels of Aβ42, TNFα or IL-1β). Moreover, exogenous $PGE_2$ prevented the restorative effects of COX-2 inhibitors on LTP, suggesting a detrimental effect of Aβ42-induced $PGE_2$ elevation on synaptic plasticity (Kotilinek et al., 2008). In contrast with the findings of this study, which suggested that the effects of COX inhibition on LTP are not related to their effects on pro-inflammatory cytokines, a previous study reported that inhibition of PG synthesis by indomethacin blocked IL-1-induced LTP inhibition (Coogan et al., 1999). Thus, in some pathological conditions elevated levels of $PGE_2$ produce detrimental effects on LTP, and at least partly mediate the detrimental effects of IL-1.

### 2.3. Detrimental effects of immune/inflammatory processes on neurogenesis

Recent findings demonstrate that various inflammatory processes, particularly microglial activation and pro-inflammatory cytokines secretion, can have a detrimental influence on neurogenesis. Many studies in this area were conducted in the context of brain injury and stroke, which produce complex short and long-term effects on neurogenesis concomitantly with alterations in inflammatory processes. Because the neurogenesis process under these conditions is fairly unique and the literature on this topic is quite extensive (Ekdahl et al., 2009), the discussion below will be limited to the detrimental effects of inflammatory processes on neurogenesis in the non-injured brain.

*2.3.1. Microglial activation*

Although under quiescent condition microglia may be involved in facilitation of neurogenesis (Section 1.3.2), inflammation-induced microglial activation has been implicated in neurogenesis suppression (Ekdahl et al., 2009; Kempermann and Neumann, 2003). Particularly convincing evidence for this notion was provided by showing that chronic intracortical LPS administration resulted in decreased neurogenesis (both basal and insult-induced). Moreover, the magnitude of LPS-induced microglial activation was negatively correlated with the generation of new neurons, and administration of the microglial inhibitor minocycline could block the anti-neurogenic effects of LPS (Ekdahl et al., 2003). Similarly, brain irradiation was also found to induce a marked hippocampal neurogenesis suppression, which was negatively correlated with the substantial levels of microglial activation (Monje et al., 2003). Interestingly, in order to affect neurogenesis, the inflammatory stimulus does not have to be localized to the brain, as even a single i.p. LPS injection increased the number of activated microglia and reduced hippocampal neurogenesis. Furthermore, *in vitro* neuronal differentiation was found to be decreased when neurons were co-cultured with activated but not resting microglia, and this effect was mediated by soluble factors, as conditioned medium from activated microglia produced the same effect (Cacci et al., 2005; Monje et al., 2003). As discussed below, these factors mainly include IL-6 and TNFα (Butovsky et al., 2006; Cacci et al., 2005; Liu et al., 2005; Monje et al., 2003). It should be noted, however, that chronic activation of microglia, either *in vitro* (Cacci et al., 2008) or *in vivo* (Bonde et al., 2006), reduces their ability to produce pro-inflammatory cytokines, and converts their phenotype to non-detrimental or even neuroprotective.

Another recent evidence for a role of microglia in neurogenesis suppression was obtained by demonstrating the influence of fractalkine (CX3C) and its receptor (CX3CR1) on hippocampal neurogenesis. Fractalkine (FKN), which is released by neurons and acts on CX3CR1 (expressed exclusively by microglia), has been shown to suppress excessive microglia activation. Importantly, mice with

impaired FKN/CX3CR1 signaling exhibit reduced neurogenesis (Bachstetter et al., in press). This reduction depends on microglial activation and the production of IL-1β, since IL-1ra administration enhanced neurogenesis in the FKN/CX3CR1 signaling impaired mice. Moreover, reversing the aging-related loss of FKN by exogenous FKN administration reversed the aging-related decrease in hippocampal neurogenesis (Bachstetter et al., in press).

In addition to affecting the neurogenesis process itself, inflammation was also found to affect the functional synaptic connectivity of new neurons generated in the adult brain. Specifically, intrahippocampal LPS administration, which produced an overall increased network activity in hippocampal neural circuitries, was found to enhance the inhibitory synaptic drive in the new cells, probably by enhancing GABAergic neurotransmission (Jakubs et al., 2008). Thus, despite the detrimental effects of the inflammatory environment on neurogenesis, a high degree of synaptic plasticity of the new neurons is preserved, which enables them to respond to the increase in excitatory input with a compensatory enhancement of inhibitory neurotransmission.

### 2.3.2. Inflammatory cytokines

*2.3.2.1. IL-1β.* Several research groups have recently provided direct evidence for the influence of IL-1β on neurogenesis. In these studies chronic or acute pharmacological administration of IL-1β (Goshen et al., 2008; Koo and Duman, 2008), as well as chronic expression of a recombinant adenoviral vector expressing human IL-1β in the hippocampal DG (Mathieu et al., 2010a) resulted in impaired hippocampal cytogenesis and neurogenesis. The effects of IL-1β on neurogenesis involve at least two mechanisms. The first is indirect, via IL-1-induced glucocorticoids secretion (Goshen et al., 2008) (this mechanism will be discussed below, see Section 2.4.2). The second mechanism involves a direct effect of IL-1 on neuronal progenitors in the sub-granular zone of the hippocampus, via the IL-1R1 which is expressed by these cells. This receptor was also shown to be expressed *in vitro*, by all proliferating primary cultured adult hippocampal progenitors (AHPs) (Koo and Duman, 2008) or embryonic cortical NPCs (Ajmone-Cat et al., 2010). The effects of IL-1 *in vitro* differed somewhat depending on its cellular targets: In the cortical NPCs culture, IL-1α strongly enhanced NPCs differentiation into astrocytes, without affecting cell viability and neuronal differentiation, whereas IL-1β had much smaller effects (Ajmone-Cat et al., 2010). In the AHPs culture, exposure to IL-1β resulted in a decreased percent of proliferating AHPs in the culture. Furthermore, this anti-neurogenic effect was found to be mediated by activation of NfκB signaling pathway, and could be blocked by IL-1ra (Koo and Duman, 2008).

Based on the similar effects of stress and IL-1 on neurogenesis and the induction of IL-1 by stress, it was recently hypothesized that IL-1 mediates the anti-neurogenic effect of stress (Ben Menachem-Zidon et al., 2008; Goshen et al., 2008; Koo and Duman, 2008). Indeed, we have recently showed that subjecting mice to chronic isolation stress produced a dramatic decrease in hippocampal neurogenesis. However, intra-hippocampal transplantation of NPCs derived from neonatal mice with transgenic over-expression of IL-1ra, which chronically elevated the levels of IL-1ra throughout the stress exposure period, completely abolished the detrimental effect of isolation stress on neurogenesis (Ben Menachem-Zidon et al., 2008). A role for IL-1 in mediating the effects of acute stress was recently demonstrated by showing that blockade of IL-1 signaling either in IL-1rKO mice or in IL-1ra-injected mice blocked the decrease in neurogenesis induced by two acute stressors (footshock and immobilization) in rats (Koo and Duman, 2008). Together, these findings indicate that elevation in hippocampal IL-1 levels can markedly suppress hippocampal neurogenesis. Such an elevation has been shown in many medical conditions (e.g., neurodegenerative diseases) as well as following exposure to acute or chronic stressors, and therefore IL-1 probably plays an important role in mediating the reduction in neurogenesis that characterizes these conditions.

*2.3.2.2. IL-6.* Along with its detrimental effects on neural plasticity, IL-6 can also inhibit neurogenesis. Transgenic expression of IL-6 in astrocytes markedly reduced hippocampal neurogenesis (Vallieres et al., 2002). Consistently, exposure to IL-6 *in vitro* decreased neurogenesis by half (Monje et al., 2003). Furthermore, several studies revealed that IL-6 is involved in mediating the anti-neurogenic effect of activated microglia on *in vitro* neurogenesis. Specifically, when NPCs were exposed to conditioned media from activated microglia, neurogenesis was markedly decreased (Monje et al., 2003), and the percent of cells expressing positive astrocytic markers was increased (Nakanishi et al., 2007). In these studies, IL-6 appeared to induce both a non-specific decrease in cell survival as well as reduced neuronal differentiation, rather than selective changes in the proliferation or death of neuroblasts or immature neurons. Neutralizing anti-IL-6 antibodies prevented the inhibitory effect of activated microglia on *in vitro* neurogenesis (Monje et al., 2003), and reduced astrocytic differentiation (Nakanishi et al., 2007).

*2.3.2.3. TNFα.* The role of TNFα in neurogenesis was assessed by several approaches. Testing the effects of TNFα exposure *in vitro* revealed marked suppression of NPCs proliferation, including reduced neurogenesis (Ben-Hur et al., 2003; Monje et al., 2003). In another study, *in vitro* TNFα exposure during NPCs proliferation did not produce any effect, but when TNFα was applied during differentiation of the neuronal precursor cells it reduced the percentage of neurons and increased the percentage of astrocytes (Keohane et al., 2010). An additional study tested the effect of different TNFα concentrations on *in vitro* neurogenesis, and found that whereas high TNFα levels caused cell death, low levels may actually promote proliferation (Bernardino et al., 2008). A second approach was to examine the role of TNFα in mediating the anti-neurogenic effects of microglial activation. Conditioned media from LPS-activated microglia was found to reduce neuronal differentiation, and this effect was at least partly mediated by TNFα because secretion of this cytokine from activated, compared to resting, microglia was increased, and pentoxifylline, a TNFα inhibitor, reduced the detrimental effect on neuronal differentiation (Liu et al., 2005). A third approach for examining the role of TNFα is to assess the neurogenesis process in mice with deletions of the two TNF receptors. Using this approach it was found that the number of new hippocampal neurons was elevated in mice with deletion of the TNF-R1 as well as mice with double knockout of both TNF-R1 and TNF-R2; however mice with deletion of the TNF-R2 only had normal neruogenesis (Iosif et al., 2006). Together these findings suggest that by signaling via the TNF receptor type I, TNFα suppresses the neurogenesis process and drives the differentiation of neural precursor cells towards an astrocytic, rather than neuronal fate.

## 2.4. Mechanisms underlying the detrimental effects of immune processes on neurobehavioral plasticity

The findings presented in this section demonstrate that elevated levels of pro-inflammatory cytokines can produce detrimental effects on learning, memory, neural plasticity and neurogenesis. To produce these effects, such high levels of cytokines should be present in the brain and influence neuronal circuits. However, the initial source of immune activation is usually peripheral. Thus, the information about this activation has to be transmitted into the brain via humoral and neural immune-to-brain communication pathways. Once this information reaches the brain, it activates

brain cells, which in turn produce and secrete pro-inflammatory mediators (Dantzer et al., 2008; Maier and Watkins, 1998). Obviously, the immune activation and cytokine secretion can be also initiated inside the brain, e.g., following brain injury, trauma, intracerebral infections or irradiation. Furthermore, exposure to psychological stress, particularly when it is severe and/or chronic, can also activate brain cells, particularly microglia (Frank et al., 2007; Nair and Bonneau, 2006; Tynan et al., 2010), and induce the production of high levels of cytokines (Goshen and Yirmiya, 2009). Stress-induced immune activation is solely initiated by neuronal activity, and probably involves the activation of noradrenergic pathways (Blandino et al., 2006, 2009; Johnson et al., 2005) as well as alterations in cholinergic neurotransmission (Cohen et al., 2003; Ofek et al., 2007; Shapira-Lichter et al., 2008). Moreover, the elevation of brain cytokines produces further activation of stress response systems, particularly the HPA axis and SNS, resulting in activation of reverberating, positive feedback loops (Fig. 3). The high levels of brain cytokines, along with the high levels of cortisol and monoamines (whose production is partially regulated by brain cytokines) activate various cellular mechanisms, which result in impaired learning and memory and suppressed neural plasticity and neurogenesis, as detailed below (Fig. 4).

*2.4.1. Neuro–glial interactions, neuronal hyper-excitability and glutamatergic neurotransmission*

Learning, memory and neural plasticity depend on highly regulated patterns of neuronal activity, which are tightly controlled in time and space. In contrast, uncontrolled, unregulated and excessive neuronal activation results in impairments in these functions and may even lead to pathological hyper-excitability, epilepsy, excitotoxicity and neurodegeneration. In Section 1, we demonstrated that a well-controlled and timed activation of immune cells and secretion of cytokines plays a beneficial modulatory role in learning, memory, neural plasticity and neurogenesis. For example, local interactions among microglia, astrocytes, T cells and neurons in the hippocampus are important for memory consolidation, high frequency stimulation-induced IL-1 production plays a facilitatory role in the development of the increased excitability characterizing LTP, and astrocytic-derived TNFα increases neuronal excitability during prolonged periods of reduced synaptic inputs, promoting synaptic scaling.

However, the intense brain immune activation and "cytokine storm" that characterizes infections, injury, neurotrauma and severe/chronic stressful conditions, can induce hyper-excitability of neuronal circuits, and eventually may elicit epileptic seizures, delirium, excitotoxicity and neurodegeneration (Fig. 5). Specifically, ample evidence indicates that inflammatory challenges, such as infectious agents (Singh et al., 2008), LPS (Galic et al., 2008; Rodgers et al., 2009), high levels of IL-1 (Balosso et al., 2008; Vezzani et al., 1999; Viviani et al., 2003), or the secretion of HMGB1 (a damage-associated molecular pattern that is secreted by hyperexcited or damaged neurons and possibly glia) (Maroso et al., 2010) activate known signal transduction pathways that induce neuronal hyper-excitability and epilepsy. These pathways include the activation of TLR4 or the IL-1 receptor, which in turn recruit the myeloid differentiation adaptor protein (MyD88), activating Src-family kinases, leading to NMDA receptor-2B (NR2B) phosphorylation and enhanced NMDA-dependent Ca2+ influx (Balosso et al., 2008; Maroso et al., 2010; Vezzani et al., 1999; Viviani et al., 2003). The threshold for the transition from the normal beneficial role of immune processes to their detrimental over-activated state may differ according to age, gender, and genetic vulnerability. For example, very young individuals, in which the brain is more plastic and the large number of newly generated neurons are more excitable, are also more susceptible to inflammation-induced hyper-excitability and febrile seizures (Heida and Pittman, 2005).

The intense neuronal activation that occurs during epileptic seizures produces further immune (particularly microglial) activation and pro-inflammatory cytokines production (Vezzani et al., 2008). This chain of inflammatory events results in a positive feedback loop that can lead to excitotoxicity (Tikka et al., 2001) and eventually even to apoptosis and neurodegeneration (Block and Hong, 2005). Pathological hyper-excitability is associated with disturbances in learning, memory, neural plasticity and neurogenesis (Katagiri et al., 2001; Lowenstein et al., 1992). This can be exemplified by the finding that transgenic mice with over-expression of either TNFα or IL-6, display learning and memory disturbances (Fiore et al., 2000, 1996; Heyser et al., 1997) concomitantly with increased sensitivity to seizures (Akassoglou et al., 1997; Samland et al., 2003). In vulnerable individuals (particularly when the brain immune system is already primed due to normal aging or neurodegenerative conditions) inflammation-induced hyper-excitability results in delirium, which further reduces cognitive functioning (Murray et al., 2010; van Gool et al., 2010). Furthermore, when the inflammatory conditions produce excitotoxicity, apoptosis and neurodegeneration, an even greater impairment in neurobehavioral plasticity ensues (Selkoe, 2002).

Studies on the role of glutamatergic neurotransmission in cytokine-mediated impairments of LTP reveal an additional level of complexity in the above-presented view. In these studies, IL-1β administration *in vivo* was found to increase the *in vitro* release of glutamate from synaptosomes prepared from the DG of rats (Vereker et al., 2000). This finding is consistent with the above presented view of inflammation-induced neuronal hyper-excitability, although it should be noted that a subsequent experiment with LPS did not show such an effect (Kelly et al., 2003). However, these and several additional studies also reported that in synaptosomes that were exposed (*in vitro*) to KCl or 4-aminopyridine (neuronal activators known induce a marked glutamate release), IL-1β, IL-6 or LPS completely abolished the increased glutamate release (D'Arcangelo et al., 2000; Kelly et al., 2003, 2001; Vereker et al., 2000). Consistently with these findings, exposure to IL-1β was found to decrease tetanic stimulation-induced calcium influx in hippocampal slices (Cunningham et al., 1996; Plata-Salaman and Ffrench-Mullen, 1992, 1994), probably via effects on NMDA receptors (Coogan and O'Connor, 1997). Interestingly, aged rats (in which pro-inflammatory cytokine levels are chronically elevated) also display decreased KCl-induced glutamate release, similarly to young rats treated with IL-1 (Murray and Lynch, 1998; O'Donnell et al., 2000).

It is somewhat difficult to integrate the findings on the hyper-excitability, epilepsy and excitotoxicity that are produced by brain inflammation *in vivo* and the findings from cytokine-induced alterations in slice and synaptosomal preparations, *in vitro*. However, together these findings suggest that on the background of an inflammatory, hyper-excitable condition, the effects of acute neuronal stimulation *in vitro*, and possibly also tetanic or high frequency stimulation *in vivo*, are diminished by cytokines that comprise the inflammatory response, and therefore, the development of neural plasticity, learning and memory are impaired.

*2.4.2. Activation of the HPA axis*

As mentioned in Section 1.4.1, stress-induced secretion of glucocorticoids and monoamines (norepinephrine, dopamine and serotonin) can facilitate memory consolidation (McGaugh, 2000). However, under severe stressful conditions, over-activation of the HPA axis results in learning and memory impairment (de Kloet et al., 1999; Kim and Diamond, 2002; McEwen and Sapolsky, 1995). Similarly, the effects of peripheral corticosterone on hippocampal neural plasticity also follow an inverted U-curve (Diamond et al., 1992). Under high stress conditions, intense activation of the noradrenergic system, acting via the α1-adrenergic receptors, can

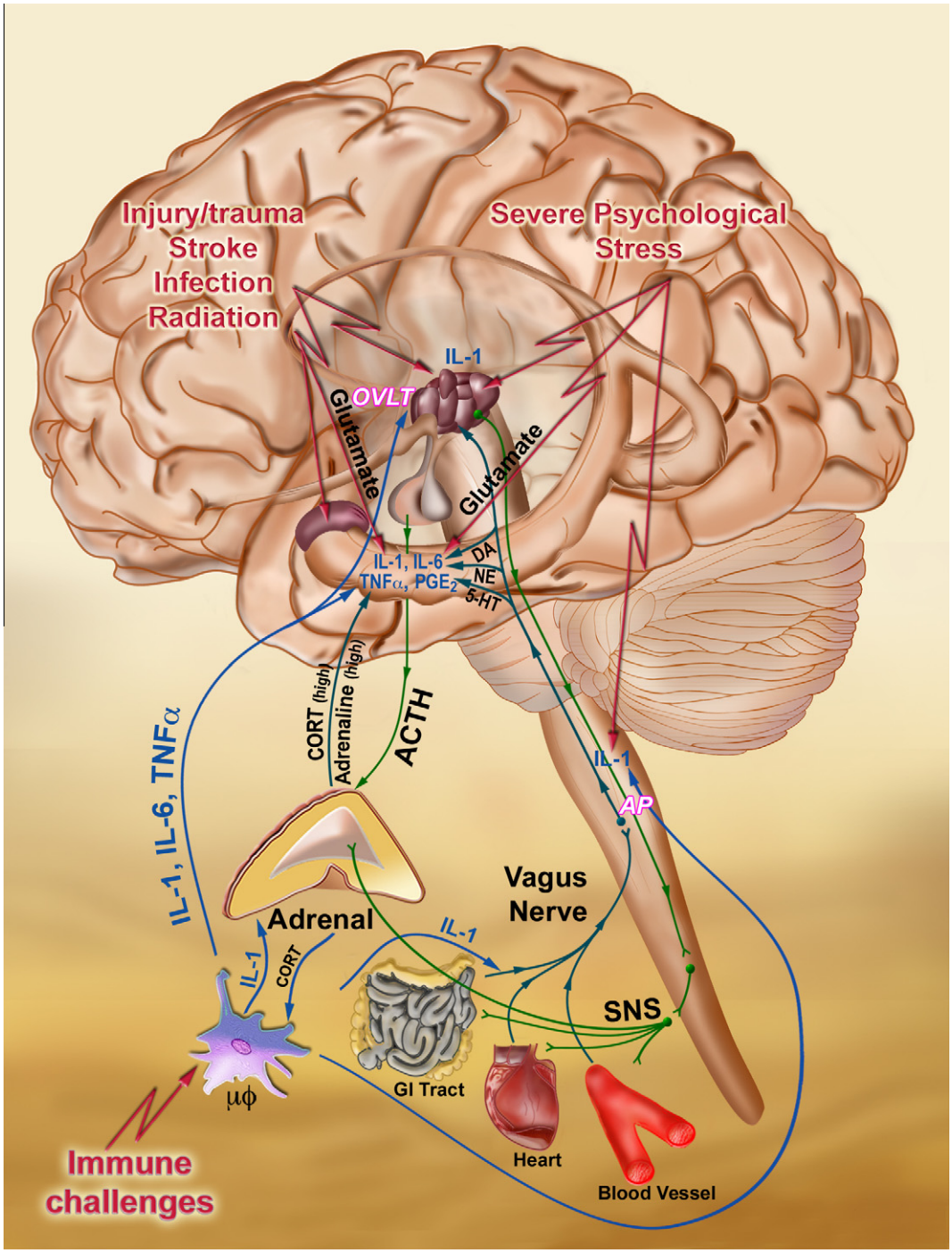


**Fig. 3.** A systemic model of the detrimental role of immune processes in behavioral and neural plasticity. During infection or injury, either in the periphery or within the brain (including trauma, stroke and radiation), as well as following exposure to severe psychological stress, several components of the immune system are stimulated and the brain is washed by high levels of pro-inflammatory cytokines (particularly IL-1, IL-6, TNFα) and $PGE_2$. The production of these compounds in various brain areas, including the hippocampus, hypothalamus and brain stem, is induced in microglia and astrocytes by the increased glutamatergic inputs (mainly from various cortical areas), as well as by elevated monoaminergic neurotransmission (i.e., noradrenergic, serotonergic and dopaminergic pathways arising from the brain stem). In addition, peripheral immune cells, such as macrophages (μφ) produce and secrete IL-1 and other inflammatory cytokines, which influence various cellular components in the brain. This influence is exerted by immune-to-brain communication mechanisms, including humoral pathways (e.g., action of blood–borne cytokines via circumventricular organs, such as the OVLT near the hypothalamus and the area postrema (AP) in the brain stem) and neural pathways (e.g., via IL-1-inudced activation of the vagus nerve). The inflammatory cytokines play an important role in activation of the HPA axis and the SNS, resulting in the production of high levels of cortisol (or corticosterone in rodents), adrenaline, and intense afferent activation of brain monoaminergic systems, which have detrimental effects on memory functioning, synaptic plasticity and neurogenesis.

also exert a debilitating effect on memory performance (Berridge and Waterhouse, 2003).

Because microglial activation and brain cytokines are major inducers of the HPA axis, several studies examined the possible involvement of CRF and GCs in the memory impairments induced by inflammatory challenges. An involvement of GCs was suggested by two studies (Song and Horrobin, 2004; Song et al., 2004a), reporting a detrimental effect of intracerebral administered IL-1β on spatial memory in the water maze as well as on working memory in the radial arm maze, concomitantly with corticosterone elevation. Eight weeks of feeding with a diet enriched in the anti-inflammatory compound omega-3 fatty acid ethyl-eicosapentae-

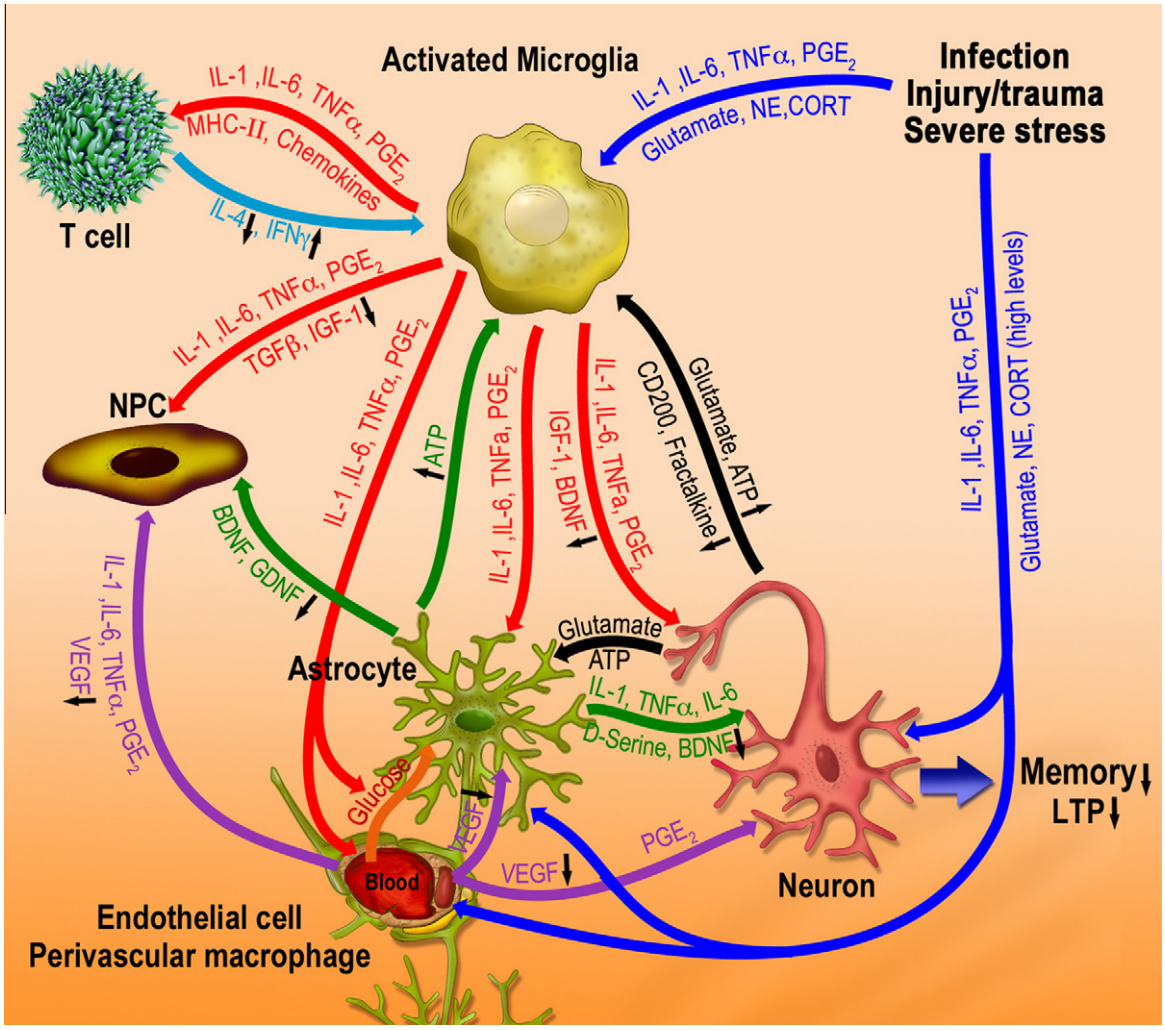


**Fig. 4.** A molecular/cellular model of the role of immune processes in memory loss and suppressed neural plasticity due to infection, injury and severe stress. Infection, injury or severe stress produce marked elevation in hippocampal pro-inflammatory cytokines and mediators, facilitated by strong glutamatergic, monoaminergic and adrenocortical inputs (blue arrows). These inputs strongly activate microglia and astrocytes within the hippocampus, which change their morphology and functioning and further secrete high levels of pro-inflammatory cytokines and $PGE_2$ (red and green arrows, respectively). Reduced production by neurons of compounds that keep microglia in relative quiescence under normal conditions (CD200 and fractalkine) (black arrows) also contributes to microglial activation. Additional cytokines and particularly $PGE_2$ are also produced by endothelial cells and perivascular macrophages (purple arrows). T cells, on the other hand produce less IL-4 and more IFNγ, contributing to the microglial activation (light blue arrow). The over-production of high levels of pro-inflammatory cytokines breaks the delicate balance needed for the actions of these compounds during normal learning and LTP, and can produce direct detrimental effects on neuronal functioning and the proliferation and differentiation of neural precursor cells (NPC), resulting in suppressed neurogenesis. In addition, proinflammatory cytokines reduce the production of plasticity-related molecules, particularly growth factors, such as BDNF, IGF-1, VEGF, TGFβ and GDNF. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

noic acid (E-EPA, 1%) attenuated the IL-1-induced memory impairment, and blocked the IL-1-induced increase in serum corticosterone concentration (Song and Horrobin, 2004; Song et al., 2004a). A more direct evidence for the involvement of adrenocortical activation in the effect of IL-1 on memory was provided by showing that IL-1-induced memory impairment in the radial arm maze was blocked when IL-1 was co-administered with the GC receptor antagonist RU486 (Song et al., 2004b).

CRF may be also involved in mediating the effects of inflammatory challenges on memory, as evidenced by the finding that inhibition of CRF-1 receptors by antalarmin ameliorated the learning deficits induced by LPS, while reducing LPS-induced hippocampal (but not peripheral) IL-1β production (Kohman et al., 2007). At present, no studies tested the role of over-activation of monoaminergic pathways in mediating the effects of inflammatory processes on learning, memory and neural plasticity.

Ample evidence indicates that elevated levels of glucocorticoids inhibit hippocampal neurogenesis. In particular, impaired hippocampal neurogenesis has been reported following exposure to various acute and chronic stress protocols, as well as to corticosterone administration (Deng et al., 2010; Leuner and Gould, 2010). As mentioned above, we have recently found that IL-1 induced corticosterone secretion plays an important role in stress-induced neurogenesis suppression. Specifically, we reported that IL-1rKO mice displayed neither corticosterone secretion nor neurogenesis suppression following exposure to chronic stress. Consistently, removal of endogenous glucocorticoids by adrenalectomy also abolished the anti-neurogenic effects of chronic stress, whereas chronic administration of corticosterone for 4 weeks produced neurogenesis suppression in both WT and IL-1rKO mice (Goshen et al., 2008).

*2.4.3. Suppression of neurotrophins production*

Neurotrophic factors mediate some of the beneficial effects of homeostatic immune processes on neural and behavioral plasticity, as described in Section 1.4.3.3. However, when the immune system is strongly activated, during disease or stress, the secretion of neurotrophic factors is inhibited, rather than enhanced, and this

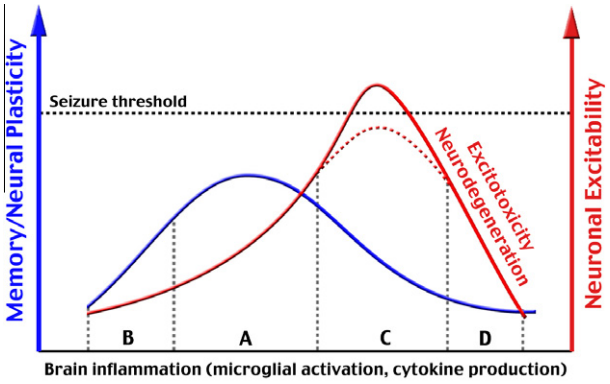


**Fig. 5.** Memory, neural plasticity and neuronal excitability as a function of brain inflammation. Immune processes in the brain, including microglial activation and inflammatory cytokine production play a complex dual role in learning, memory, and neural plasticity (blue graph), as well as neuronal excitability (red graph). Locally controlled and properly timed activation of immune processes (e.g., IL-4 secretion by T cells and its effects on microglia, IL-1 secretion and its effects on astrocytes and other brain cells, TNFα secretion by astrocytes during periods of prolonged reduction in neuronal inputs) is involved in the increased neuronal excitability that underlies neural plasticity (e.g., the development of LTP, synaptic scaling) and memory consolidation (section A in graph). Any deviation from the physiological range, either by excessive immune activation or by immune suppression, results in memory and plasticity impairments: Insufficient activation of immune parameters, exemplified by genetic models of immune/cytokine deficiency (such as SCID, nude, IL-1rKO and IL-1raTG mice) or treatment with immune-suppressive drugs, produces impairments in learning and memory, associated with reduced excitability, inability to mount LTP and suppressed neurogenesis (section B in graph). On the other hand, the intense brain immune activation and "cytokine storm" that characterizes infections, injury, and exposure to extreme stress, can induce hyper-excitability of neuronal circuits, which eventually may elicit epileptic seizures (although it does not necessarily reach the epileptic seizures threshold, as signified by the dashed line). The inflammation-induced pathological hyper-excitability is associated with disturbances in learning, memory, and neural plasticity (section C in graph). If the immune over-activation is even more severe and/or chronic, excitotoxicity, apoptosis and neurodegenearation may ensue, resulting in reduced neuronal excitability and further impairments in learning, memory and neural plasticity (section D in graph). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

may underlie the detrimental effect of inflammatory challenges on memory and plasticity.

*2.4.3.1. BDNF.* As described above (Section 1.4.3.3), BDNF has been implicated in hippocampal-dependent memory (Barnes and Thomas, 2008; Heldt et al., 2007), LTP (Lu et al., 2008) and neurogenesis (Li et al., 2008). Whereas enhanced BDNF signaling seems to contribute to the beneficial effects of immune parameters on learning and memory, several lines of evidence suggest that reduced BDNF signaling underlies the detrimental involvement of immune processes in neural plasticity: (1) Reduced hippocampal BDNF is exhibited by SCID mice, as well as mice with transgenic excess of T cells directed against an irrelevant (non-self) antigen, both of which exhibit impaired hippocampal-dependent learning, memory and neurogenesis. (2) Intra-hippocampal LPS injection activates microglia and increases IL-1β and TNFα production, while reducing the expression of BDNF and its receptor, TrkB (Tanaka et al., 2006). (3) Administration of the neuropeptide Neuromedin U blocks the detrimental effect of intracerebral administration of LPS on memory functioning while increasing the expression of BDNF in the hippocampus (Iwai et al., 2008). (4) Adult rats that suffered from a bacterial infection as neonates, display impaired fear conditioning upon a peripheral immune challenge in adulthood, accompanied by exaggerated hippocampal IL-1β response and reduced BDNF expression (Bilbo et al., 2008). (5) Hippocampal BDNF expression following contextual learning is blocked by intra-hippocampal IL-1β administration (Barrientos et al., 2004). (6) The detrimental effect of stress-induced IL-1 on memory seems to be mediated by a reduction in BDNF levels, as exposure to social isolation reduced both memory functioning and BDNF expression in the DG and CA3 regions of the hippocampus, but these reductions were blocked by intra-hippocampal administration of IL-1ra before the isolation period (Barrientos et al., 2003). Similarly, CMS concomitantly caused impaired memory, increased IL-1β and TNFα levels in the plasma, and reduced hippocampal BDNF expression (Li et al., 2008).

Together, these converging lines of data suggest that a reduction in hippocampal BDNF expression may underlie the detrimental effect of immune activation on memory. It should be noted, however, that most of the findings in this area are correlational and do not provide unequivocal proof for causality. Moreover, not all findings in this area are consistent with a role for BDNF; for example, in one study a dose of LPS that was sufficient to cause marked deficits in spatial learning in the water maze, had no effect on BDNF expression in the rat DG (Shaw et al., 2001). Furthermore, in two lines of mice with transgenic over-expression of TNFα, which displayed some indication of impaired performance in the water maze test (Fiore et al., 1996), BDNF levels did not vary in a systematic anatomical manner (i.e., its levels in the hippocampus were lower in one but not the second transgenic line, were increased in the hypothalamus of both lines and increased in the cortex of the second line) (Aloe et al., 1999a,b).

*2.4.3.2. NGF.* Nerve growth factor (NGF) plays an important role in memory and synaptic plasticity. Specifically, NGF is induced following memory consolidation and LTP, and memory is impaired following NGF blockade. LTP is also impaired in NGF deficient rats, and i.c.v. injection of NGF reverses this impairment. Furthermore, NGF infusion improved hippocampal LTP in both cognitively impaired and normal rats (Conner et al., 2009; Kelly et al., 1998; Woolf et al., 2001).

Several studies suggest that reduced NGF levels may be involved in the detrimental effects of cytokines on learning and memory. A recent study demonstrated that concomitantly with its detrimental effect on memory in the 8-arm maze paradigm, i.c.v. administration of IL-1β also markedly inhibited hippocampal NGF mRNA expression. Furthermore, treatment with a diet containing ethyl-eicosapentaenoate (which is known to have anti-inflammatory effects) blocked the effects of IL-1β on NGF expression, along with its beneficial effect on memory functioning (Taepavarapruk and Song, 2010).

Several studies suggest that NGF is involved in TNFα-induced modulation of memory. Specifically, TNFαKO mice, which demonstrated enhanced memory performance, were also found to exhibit increased expression of NGF following performance of the learning task (Golan et al., 2004). Moreover, mice from two lines with transgenic overexpression of TNFα, which showed some indication of impaired performance in the water maze paradigm (Fiore et al., 1996), also demonstrated decreased hippocampal NGF secretion (Aloe et al., 1999a,b). Reduced NGF levels may also underlie the detrimental effect of high IL-1 levels on memory, as suggested by the finding that i.c.v. injection of IL-1β produced a spatial memory deficit concomitantly with reduced hippocampal NGF mRNA expression (Taepavarapruk and Song, 2010).

*2.4.4. Alterations in cholinergic neurotransmission*

Cholinergic neurotransmission plays a critical role in learning, memory and neural plasticity (Everitt and Robbins, 1997). The cholinergic system and inflammatory cytokines are inter-related in complex feedback loops. For example, inflammatory challenges, including exposure to IL-1β, activate the acetylcholine (ACh) hydrolyzing enzyme acetylcholinesterase (AChE), and therefore

can reduce cholinergic neurotransmission (Li et al., 2000; Ofek et al., 2007; Shapira-Lichter et al., 2008). Since both in the periphery and the brain ACh produces anti-inflammatory effects (Pollak et al., 2005; Tracey, 2002), elevation of AChE activity can produce further cytokine secretion and such effects were suggested to be involved in stress- and endotoxin-induced memory disturbances in humans (Cohen et al., 2003; Ofek et al., 2007; Shapira-Lichter et al., 2008) A recent study provided further evidence for this hypothesis, demonstrating that i.c.v. administration of IL-1β in rats suppressed hippocampal ACh release in a glucocorticoid-dependent manner (i.e., this suppression could be blocked by RU486 administration). Furthermore, the effect of IL-1β on ACh release was correlated with its detrimental effect on memory functioning in the 8-arm radial arm maze, and both effects could be inhibited by ethyleicosapentaenoate diet, which reduces inflammatory reactions (Taepavarapruk and Song, 2010).

#### *2.4.5. Alterations in plasticity related IEGs and intracellular mechanisms*

As stated above, the immediate early gene Arc is critically involved in learning, memory and synaptic plasticity (Guzowski et al., 2001). Two recent studies suggest that suppression of Arc mediates the detrimental effects of infection and IL-1 on memory. In one study, infection with *E. coli*, which markedly impaired contextual fear conditioning, also suppressed basal and conditioning-induced Arc expression in the hippocampus. Furthermore, IL-1ra administration blocked both the infection-induced memory disturbances and the suppression of Arc expression (Frank et al., 2010). In the second study, mice with transgenic hippocampal overexpression of IL-1β, which resulted in impaired long-term contextual and spatial memory, were also found to display reduced basal and conditioning-induced levels of Arc (Hein et al., 2010).

The intracellular signal transduction pathways that mediate the detrimental effects of inflammatory challenges were examined only in the context of studies on LTP (Pickering and O'Connor, 2007). In general, the detrimental effect of LPS, IL-1β or TNFα on LTP were found to be mediated by an increase in superoxide dismutase activity and ROS production, along with activation of the MAP kinase cascade, including increases in the levels of the stress related MAP kinases c-Jun NH2-terminal kinase (JNK) and p38, as well as activation of the transcription factor nuclear factor kappa B (NFκB). These signaling mechanisms result in alteration in glutamate release and its functioning at the NMDA receptor, as described above. Interestingly, the same processes seem to be activated by environmental or physiological conditions that enhance brain cytokine levels, including aging and exposure to stress.

This scenario is supported by the following experimental lines of evidence: (1) The suppression of LTP following peripheral or central administration of LPS or IL-1β is accompanied by an increase in superoxide dismutase activity and ROS levels (Vereker et al., 2001, 2000). Moreover, application of the antioxidant phenylarsine oxide (Vereker et al., 2001) as well as feeding a diet enriched in the antioxidant vitamins A and C (Vereker et al., 2000) blocked the suppressive effects of IL-1β on LTP. Treatment with the anti-inflammatory cytokine IL-10 also reversed IL-1β-induced LTP inhibition while attenuating the stimulatory effect of IL-1β on superoxide dismutase activity and ROS production (Kelly et al., 2001). (2) Concomitantly with its inhibitory effect on LTP, i.c.v. administration of IL-1β increased p38 MAP kinase activity in DG synaptosomes (Kelly et al., 2003; Vereker et al., 2000). Co-administration of IL-1 together with the p38 inhibitor SB203580 attenuated the detrimental effect of IL-1 on LTP both *in vivo* (Kelly et al., 2003) and *in vitro* (Coogan et al., 1999), and restored KCl-induced glutamate release in IL-1-treated rats (Kelly et al., 2003). Similarly to IL-1β, TNF-α induces p38 MAP kinase activation in the DG (Butler et al., 2004). However, p38 MAP kinase seems to mediate primarily the initial inhibitory effect of TNFα on LTP, as its inhibitor SB203580 completely blocked TNFα-induced early-phase LTP impairment (1 h following tetanic stimulation), but only partially blocked the negative effect of TNFα 3 h following tetanic stimulation (Butler et al., 2004; Pickering et al., 2005). (3) Another stress activated kinase whose activity is increased by IL-1β treatment is JNK (Curran and O'Connor, 2003; Vereker et al., 2000). Moreover, the administration of the anti-inflammatory cytokine IL-10 blocked the IL-1-induced JNK activation (Kelly et al., 2001) and the JNK inhibitor SP600125 blocked the inhibitory effect of both IL-1β and TNFα on LTP (Curran and O'Connor, 2003). (4) IL-1β also increased NFκB activation in the hippocampus, and co-administration of the NFκB inhibitor SN50 attenuated the detrimental effect of IL-1 on LTP and restored KCl-induced glutamate release (Kelly et al., 2003). (5) The effects of IL-6 seem to be mediated by somewhat different signal transduction mechanisms: IL-6 application to hippocampal slices resulted in increased STAT3 tyrosine phosphorylation and reduced activation of the MAP kinases ERK1 and ERK2 (D'Arcangelo et al., 2000; Tancredi et al., 2000), which play an important role in LTP maintenance (Kelleher et al., 2004). (6) Stress- and aging-induced LTP impairment appears concomitantly with an increase in IL-1β levels and ROS production (O'Donnell et al., 2000; Vereker et al., 2001), along with increases in the levels of JNK and p38 (O'Donnell et al., 2000). (7) The inhibitory effects of both stress and aging on LTP were abrogated by dietary antioxidant supplementation with vitamins E and C or the free radical scavenger α-lipoic acid (McGahon et al., 1999; Vereker et al., 2001).

## 3. Conclusions and perspective

In the present review we attempted to provide an integrative view of the role of the immune system in behavioral and neural plasticity. The main theme arising form the available data is that during normal, quiescent periods, the immune system positively regulates learning, memory, neural plasticity and neurogenesis. This modulation is exerted via interactions among neurons, glia and other brain cells, which are highly regulated and limited in time and space to specific brain circuits. In particular, the data suggests that during learning neural inputs activate brain immune cells (particularly T cells and microglia) via neurotransmission and neurohormonal pathways. These cells, in turn, promote plasticity-related processes in neurons, astrocytes and neural precursor cells via the secretion of various mediators, including inflammatory cytokines and neurotrophic factors. These interactions culminate in the consolidation of long-term memory (particularly declarative and spatial memory, which depend on hippocampal functioning) as well as in facilitation of neurogenesis. When the immune system is strongly activated by endogenous stimuli (e.g., injury, stroke, autoimmune processes) or exogenous challenges (e.g., pathogens or severe psychological stressors), the delicate balance between the various neuro-glial interactive components that regulate normal brain functioning is interrupted. The cytokine storm that characterizes such conditions can impair all of the processes in which the immune system plays a beneficial role during quiescent conditions, resulting in impaired memory, neural plasticity and neurogenesis.

The transition from the beneficial effects of immune processes, which support memory, neural plasticity and neurogenesis, to the detrimental effects of immune processes, which characterize infectious, traumatic and severe stressful conditions, is still not well understood, either conceptually or mechanistically. One possible explanation for this transition is that the hyper-excitability induced during brain inflammation represents "too much of a good thing". According to the data presented in Part I of this review,

immune mechanisms increase neuronal excitability in a location and time limited manner by supporting LTP and neurogenesis (in which new neurons are generated with hyper-excitable properties). However, during inflammatory conditions, these immune-mediated increases in excitability may become very large, resulting in a generalized hyper-excitable condition (see Section 2.4.1 above). Because neuronal hyper-excitability is potentially very dangerous to the brain, and may lead to epilepsy, delirium, excitotoxicity, apoptosis and neurodegeneration, homeostatic mechanisms have evolved to counteract this danger. Thus, the decreases in the ability to induce LTP, the suppressed neurogenesis and alterations in the properties of new neurons, which promote their inhibitory drive, as well as the reductions in neurotrophic factors and other plasticity-related molecules may represent an adaptive strategy to prevent inflammation-associated hyper-excitability and its devastating consequences. Inflammation-induced high levels of glucocorticoids may serve as one mechanism that underlies these counteractive defensive responses. Direct inhibitory effects of high (in contrast to low) cytokines levels on neuro-plasticity mechanisms may also serve the same purpose.

Impairments in learning and memory may represent the "price" for these counteractive excitability-reducing measures. Alternatively, it may be argued that under inflammation-induced hyper-excitable conditions learning and memory would be susceptible to errors, and the danger of forming irrelevant associations would exceed the benefit of forming meaningful ones. Therefore, under transient inflammatory conditions even the impairments in learning and memory may be regarded as an adaptive protective response. Obviously, when the inflammatory condition becomes chronic, and particularly if it involves neurodegenerative processes, the loss of memory, neural plasticity and neurogenesis becomes incompatible with functioning and adaptation to the environment, leading to neuro- and psycho-pathology.

Although the view presented in this perspective, and in the entire review is supported by fair amount of data, much more research is needed to elucidate conceptual and mechanistic issues pertaining to the role of the immune system in neurobehavioral plasticity, because only deep understanding of this role will allow rational development of memory boosting procedures for normal healthy individuals, as well as preventive and therapeutic procedures for disorders involving memory loss and reduced neuroplasticity and neurogenesis.

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