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Review

Evidence for a cytokine model of cognitive function

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ABSTRACT

Aiming at a formulation of a cytokine model of cognitive function under immunologically unchallenged physiological conditions, this article reviews the cytokine biology in the central nervous system (CNS) and recent developments in normal cytokine functions within the CNS that subserve cognitive processes. Currently available evidence shows that the cytokines IL-1β, IL-6 and TNF-α play a role in complex cognitive processes at the molecular level, such as synaptic plasticity, neurogenesis, as well as neuromodulation. Such findings provide evidence for a cytokine model of cognitive function, which shows that cytokines play an intimate role in the molecular and cellular mechanisms subserving learning, memory and cognition under physiological conditions. These cytokine-mediated cognitive processes have implications in the long-term development and pathogenesis of specific neuropsychiatric disorders such as major depression and dementia. The identification of this central role of cytokines in various brain activities during health provides greater insight into normal brain functions, especially synaptic plasticity, memory and cognition, and facilitates the understanding of specific biological mechanisms involved in neuropsychiatric diseases, such as dementia and depression. In order to extend the suggested cytokine model of cognitive function onto other members of the cytokine family, future research is required to investigate the physiological effects of other cytokines such as interferon-gamma (IFNγ), alpha(1)-antichymotrypsin and IL-2 on cognitive function at the molecular level under immunologically unchallenged conditions.

Contents

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1. Introduction

The interactions between the immune and central nervous systems (CNS) in pathological states such as multiple sclerosis and depression have long been under investigation. In recent years, the discovery of multiple functions of cytokines in the central nervous system suggests that cytokines play a central role in complex CNS functions such as cognition (Hopkins and Rothwell, 1995; Pollmacher et al., 2002; Rothwell, 1999; Rothwell and Hopkins, 1995; Wilson et al., 2002). Most notably, the over-expression of cytokines has been associated with numerous pathological states (both within the central and peripheral nervous system), such as infection (viral, bacterial and fungal), autoimmune disease (i.e. multiple sclerosis), stroke, trauma, neurodegenerative disease (i.e. Alzheimer's disease (AD) and other dementias) (Ransohoff and Benveniste, 2006; Rojo et al., 2008; Rothwell and Loddick, 2002; Shaftel et al., 2008; Viviani et al., 2004) and in neuropsychiatric disorders, such as depression (Anisman et al., 2008; Capuron and Dantzer, 2003; Dantzer et al., 2008; Irwin and Miller, 2007; Kronfol and Remick, 2000; Raison et al., 2006). More specifically, some cytokines, such as interleukin 1beta (IL-1-beta), interleukin 6 (IL-6) and tumor necrosis factor (TNF) have been associated with cognitive decline and dementia in several cross-sectional and prospective population studies (Dik et al., 2005; Holmes et al., 2003; Schmidt et al., 2002; Wilson et al., 2002). In addition, cytokines, such as TNF and IL-1-beta have been related to Alzheimer's disease in clinical cohorts (Dik et al., 2005; Holmes et al., 2003).

It is now believed that cytokine-mediated pathophysiological processes underlie the cognitive impairments associated with several neuropsychiatric diseases, making cytokines ideal targets for therapeutic intervention (Reichenberg et al., 2001; Tobinick, 2007; Tweedie et al., 2007; Wilson et al., 2002). Despite these pathological implications (Bitsch et al., 2000; He et al., 2007), cytokines have also been shown to exert physiological (Blatteis, 1990; Sei et al., 1995; Vitkovic et al., 2000a) and even neuroprotective (Pan and Kastin, 2001; Schwartz et al., 1991, 1994) functions.

Research by this group suggests that in healthy elderly humans cytokines, in particular interleukin 8, under physiological conditions, are possibly involved in cognitive processes such as memory, perceptual speed and motor function (Baune et al., 2008a). Moreover, this group recently reported the associations between genetic variants of cytokines (IL-1beta, IL-6 and TNF) and cognitive function in healthy elderly humans in the general population (Baune et al., 2008b). More specifically, the results suggest that genetic variants of TNF may have protective effects in cognitive function such as perceptual speed (Baune et al., 2008b). In an animal model of cytokine-mediated cognitive function such as memory and learning, we were able to demonstrate that the presence of TNF under immunologically non-challenged conditions is essential for normal functions of memory and learning (Baune et al., 2008). This research linking complex cognitive phenotypes and cytokine effects in the CNS is well based on previous evidence to suggest that cytokines play a role in normal CNS function at a cellular and molecular level (see Jankowsky and Patterson, 1999 for review). For instance, during health both IL-1 and TNF have been shown to act as neuromodulators, as well as, pro-inflammatory factors (Blatteis, 1990; Sei et al., 1995; Vitkovic et al., 2000a,b).

Although these detrimental effects on cognitive function in both over-expressing and cytokine deficient models suggest that cytokines play an important physiological role in the CNS at the molecular and cognitive level, it still remains to be fully understood as to how cytokines participate in the molecular and cellular mechanisms subserving complex CNS functions such as learning, memory and cognition. Interestingly, growing evidence suggests that in particular the cytokines IL-1, IL-6 and TNF are involved in the molecular and cellular mechanisms subserving complex cognitive processes (Pickering and O'Connor, 2007; Vitkovic et al., 2000b; Viviani et al., 2007). While direct and indirect evidences show that IL-1, IL-6 and TNF may play a major role in synaptic plasticity, long-term potentiation (LTP), neurogenesis and memory consolidation, the evidence for involvement with cognitive function is less conclusive for other cytokines such as interferon-gamma (IFNγ) (Baron et al., 2008), alpha(1)-antichymotrypsin (ACT) (Dik et al., 2005; McIlroy et al., 2000; Nilsson et al., 2004) and IL-2 (Beck et al., 2002, 2005a,b).

In this review, we propose a cytokine model of cognitive function during health under immunologically unchallenged conditions. Aiming to establish an improved understanding of cytokine-mediated cognitive function during physiological conditions, current scientific literature on cytokine biology and their related activities within the CNS during healthy immunologically unchallenged conditions was reviewed. In particular, this review primarily concentrates on the cytokines IL-1, IL-6 and TNF-α as these cytokines have been shown to be involved in the molecular mechanisms underlying learning and memory consolidation. In addition, we also review other cytokines, especially IFNγ, ACT and IL-2 which have significant implications in neurogenesis and possibly in complex cognitive processes such as learning and memory consolidation, although their potential molecular mechanisms in learning and memory are not sufficiently studied at this stage.

This approach allows the distinction between cytokines providing conclusive evidence for a cytokine model of cognitive function and those cytokines suggestive of their involvement in higher cognitive function under physiological healthy conditions. It is intended that the models of physiological cytokine activities and properties as described in this review propose a cytokine-mediated model of cognitive function that would provide further understanding into pathological consequences of cytokines during disease. Finally, this review discusses current limitations, clinical implications and future research of a cytokine model of cognitive function.

2. Molecular and cellular aspects of cognition

Cognition often refers to a collection of cognitive processes, such as attention, executive function, learning and memory, consciousness, and language. Of these cognitive processes, there has been particular interest in recent years on the involvement of cytokines in learning and memory processes. More specifically, this area of research has largely directed its efforts at clarifying the role that cytokines play in hippocampal-dependent learning and memory; i.e., spatial memory, object recognition and contextual fear conditioning. The reasons for a focus on learning and memory processes in this review are that, firstly the neuronal mechanisms underlying higher cognitive functions such attention, executive function, consciousness and language and their relationship with cytokines remain poorly understood and secondly these other higher cognitive processes appear to rely heavily on learning and memory processes. Moreover, since the hippocampal formation appears to play a major role in memory consolidation, an emphasis was placed, in this review, on how cytokines participate in the well known and extensively studied molecular and cellular processes thought to be subserving memory formation.

As a consequence, in this review we firstly focus on the involvement of cytokines in these molecular and cellular processes and secondly we emphasize on the involvement of cytokines in

learning and memory processes as the basis for the proposed cytokine model of cognitive function. A brief overview will be given on the molecular processes of memory consolidation and synaptic plasticity before evaluating and discussing the involvement of a number of cytokines in these molecular processes.

2.1. Memory consolidation and synaptic plasticity

In brief, 'memory consolidation' is the neuropsychological mechanism and/or structural changes within the brain that allows memories to be stored more permanently. Supported by neuroimaging results (i.e. Bosshardt et al., 2005; Lepage et al., 1998) it is now widely believed that activation of the hippocampal formation is associated with memory consolidation; at least for some forms of memory. In concurrence with these findings, some (Buckner, 2003; Knowlton and Fanselow, 1998; Meeter and Murre, 2005; Nadel and Moscovitch, 1997) have suggested that memory consolidation is collectively contingent on hippocampal/entrorhinal and cortical interactions.

Although the exact neurobiological mechanisms subserving memory consolidation remain to be fully understood, three proposed cellular/molecular mechanisms have received wide acceptance; Hebbian plasticity (Malenka and Bear, 2004), synaptic scaling (Burrone and Murthy, 2003; Perez-Otano and Ehlers, 2005; Turrigiano, 2007), and adult neurogenesis (Bruel-Jungerman et al., 2007a,b; Drapeau et al., 2007). Although it was widely believed that these mechanisms were independent of each other, there is now evidence showing that these different forms of synaptic plasticity are functionally linked and act as associate partners during the formation and retention of memories (see Bruel-Jungerman et al., 2007a for further details).

2.2. Hebbian synaptic plasticity – LTP and LTD

One of the earliest and most widely accepted neurobiological theories as to how memories are consolidated is Hebbian synaptic plasticity. According to this theory a synapse will be strengthened if the pre-synaptic neuron is active while the post-synaptic neuron is firing; a process called Hebbian modification (Hebb, 1949). During repeated synaptic excitations of a single synapse (sensitization) or multiple synapses simultaneously (conditioning), neurons become 'potentiated' or highly responsive, for minutes, days, or weeks. This has lead to the suggestion that long-term potentiation and long-term depression (LTD), which is, respectively, the strengthening or weakening of synaptic connectivity due to stimulation, is the underlying cellular/molecular mechanism subserving memory consolidation (Lynch, 2000; Lynch et al., 2007; Lynch, 2004; Ziemann et al., 2004). In support of this notion, research has shown that (1) the presence of LTP and LTD is widely distributed throughout the mammalian brain, especially within the hippocampus, (2) learning modifies subsequent induction of both LTP and LTD and (4) inhibition of LTP and LTD impairs memory (Lynch et al., 2007; Lynch, 2004; Malenka and Bear, 2004; Ziemann et al., 2004).

2.3. Synaptic scaling

Despite wide acceptance for Hebbian synaptic plasticity, this form of plasticity operates via positive feedback mechanisms that, if left unchecked, tend to destabilize neuronal networks over time (Perez-Otano and Ehlers, 2005; Turrigiano, 1999, 2007). In order to maintain synaptic strength and plasticity, Hebbian plasticity requires the regulation of synapse-specific LTP and LTD at both the cell-wide and network level (Abbott and Nelson, 2000). A non-Hebbian form of synaptic plasticity, called homeostatic synaptic scaling, appears to serve this function. During prolonged periods of inactivity or hyperactivity, homeostatic synaptic scaling stabilizes the activity of neurons and networks (Abbott and Nelson, 2000; Burrone and Murthy, 2003; Echegoyen et al., 2007; Perez-Otano and Ehlers, 2005; Turrigiano, 2007), thus facilitating Hebbian synaptic plasticity, and possibly memory consolidation (Renart et al., 2003).

2.4. Neurogenesis and memory

There is also considerable evidence to suggest that adult neurogenesis plays an important role in memory consolidation, and hippocampal-dependent learning (Bruel-Jungerman et al., 2006, 2007a,b; Drapeau et al., 2007; Saxe et al., 2006; Snyder et al., 2001). For instance, research by Dupret et al. (2007), suggests that spatial learning involves learning-induced regulation of new hippocampal neurons, in which both the removal (i.e. apoptosis) and addition (neurogenesis) of hippocampal neurons contribute to memory formation. However, research by Shors et al. (2002) and Saxe et al. (2007), suggests that neurogenesis may be associated with some forms of hippocampal-dependent memory but not others. The exact mechanisms by which neurogenesis facilitates memory formation remains to be fully understood. Moreover, future research is also needed to clarify the relationship between neurogenesis and both Hebbian and non-Hebbian forms of synaptic plasticity.

3. Cytokine model of cognition

Interestingly, both the over-expression and absence of cytokines have been shown to directly influence hippocampal-dependent forms of memory and various forms of synaptic plasticity. Although the exact mechanisms as to how cytokines participate in the molecular and cellular processes thought to be subserving memory formation remains to be fully understood, significant advances have been made in elucidating these cytokine-mediated molecular and cellular processes. This section will therefore concentrate on what is known about cytokine-mediated neuronal plasticity and how these processes might influence memory and cognition. In particular, this section will focus on IL-1β, TNFα and IL-6, which have been the subject of extensive scientific investigation in this context. In addition, the potential involvement of other cytokines such as IFNγ, ACT and IL-2 are evaluated and discussed in this context. Other possible mechanisms as to how cytokines might influence cognitive processes will also be given based on the known biological properties of cytokines. Moreover, for the sake of clarity, a brief introduction will be given on each cytokine and their associated receptors.

3.1. IL-1 influences cognitive function by affecting long-term potentiation and possibly neurogenesis

The IL-1 family of cytokines is a growing cytokine family, which hitherto consists of the following cytokines, IL-1α (IL-1F1), IL-1β (IL-1F2), IL-1 receptor antagonist (IL-1ra or IL-1F3), IL-18 (IL-1F4) and IL-1F5-10. IL-1α and IL-1β display high sequence homology, and both exist as inactive forms (pro-IL-1α and pro-IL-1β) until they are cleaved by calpain and caspase-1, respectively. Once cleaved, biologically activate IL-1α remains intracellular, whereas, IL-1β is secreted by a non-classical pathway. To date, two membrane-bound IL-1 receptors, type 1 (IL-1 R1) and type 2 (IL-1 R2), have been shown to bind IL-1α, IL-1β and IL-1ra. Although, IL-1α and IL-1β bind to both receptors, evidence suggests that IL-1 R1 mediates all of the responses of IL-1, whereas,

IL-1 R2 appears to have no signalling properties (Colotta et al., 1993, 1994). It has also been shown that IL-1 R1 has a higher binding affinity for IL-1ra then both IL-1α and IL-1β, whereas, IL-1 R2 displays a higher binding affinity for IL-1β than IL-1α. Such binding and receptor properties allow IL-1ra to act strongly as an IL-1 antagonist. Moreover, since IL-1 R2 lacks signalling properties and has a high binding affinity for IL-1β, IL-1 R2 is believed to regulate IL-1 activity, especially IL-1β, by functioning as a decoy receptor (Colotta et al., 1993, 1994; Re et al., 1996). Both IL-1 R1 and IL-1 R2 can exist as soluble receptors after shedding. Although both soluble forms were originally believed to act antagonistically by sequestering biologically active and pro-IL-1, it is now believed that soluble IL-1 R1 (sIL-1 R1) can initiate signal transduction by binding to IL-1R accessory protein (Allan et al., 2005). Although the exact role in which these signalling and antagonistic mechanisms might play in central nervous system function remains to be fully understood, one possibility is neuromodulation or synaptic plasticity.

Previous research has suggested that IL-1β can modulate synaptic transmission in the hippocampus and appears to inhibit LTP induction (Bellinger et al., 1993; Cunningham et al., 1996; Katsuki et al., 1990; Murray and Lynch, 1998). Failing to confirm such findings, Schneider et al. (1998) demonstrated that increased local production of IL-1β in the hippocampus plays a role in LTP maintenance. As noted by Schneider et al. (1998), this alternative finding might have occurred because of the high concentration levels used in previous studies, which were more comparable to levels seen during pathological and inflammatory states then normal physiological conditions. Subsequent work (i.e. Coogan et al., 1999; Ross et al., 2003) has confirmed that at least under physiological conditions IL-1β is required for LTP maintenance, whereas, higher concentration of IL-1β, under pathophysiological conditions, inhibits LTP. Together these findings suggest that IL-1 plays an intimate role in synaptic plasticity and that through these mechanisms possibly an important role in memory consolidation (see Fig. 1).

Cognitive-behavioural studies in animals (see Table 1 for details) have repeatedly shown that IL-1β influences various types of hippocampal-dependent memory (Brennan et al., 2003; Yirmiya et al., 2002). Moreover, research by Depino et al. (2004), has recently demonstrated that endogenous IL-1α also participates in hippocampal memory processing. As reviewed by Pugh et al. (2001), there is considerable evidence to suggest that IL-1 might under physiological conditions play a role in memory consolidation processes. However, during stress, aging and disease, IL-1 appears to elicit memory impairment (Pugh et al., 2001). In support of these findings, IL-1β has recently been demonstrated to play a dual role in hippocampal-dependent memory processes (Avital et al., 2003; Goshen et al., 2007b). More specifically, it was demonstrated by these authors that the involvement of IL-1β in hippocampal-dependent memory follows an inverted U-shape pattern, in that basal levels of IL-1β are required for normal memory function, and any deviation from this physiological range (either deletion or elevation) results in impaired memory (Avital et al., 2003; Goshen et al., 2007b). Research by Avital et al. (2003), further demonstrated that impaired memory in IL-1 receptor type 1 knockout mice, coincided with deficits in synaptic plasticity. Moreover, as recently shown by Young et al. (2007, #234), increased levels of IL-1 disrupts an LTP-associated spinal learning paradigm (Grau et al., 2006), suggesting that IL-1 over-expression might impair LTP-associated learning processes possibly throughout the neuroaxis (Deak, 2007). Although not fully understood, these findings provide strong evidence to support a direct link between synaptic plasticity, IL-1 and cognitive functioning.

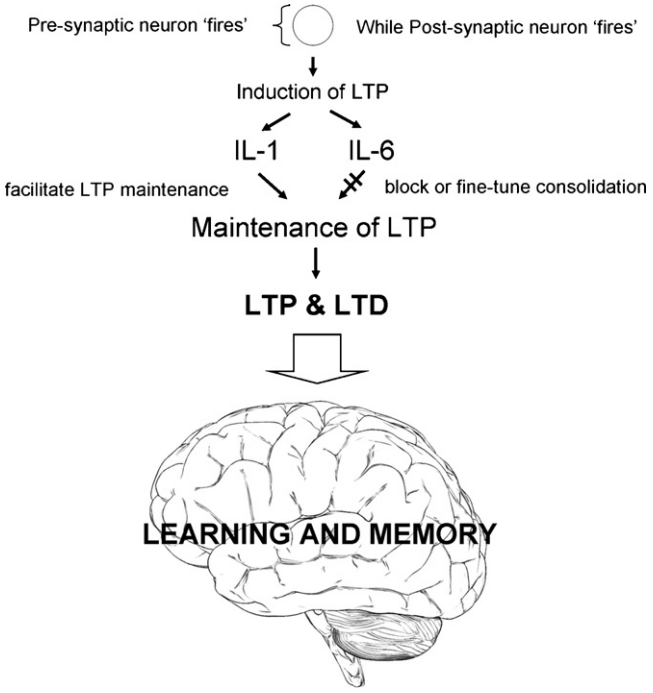

Fig. 1. Schematic illustration of the involvement of IL-1 and IL-6 in Hebbian synaptic plasticity, such as LTP and LTD. Essentially this process can be divided into three stages. In stage 1, the simultaneous neuronal activity (firing) of both pre-synaptic and post-synaptic neurons results in the induction of LTP. This induction of LTP leads to the production of both IL-1 and IL-6 (stage 2). Finally in stage 3, LTP maintenance is fine-tuned by the overall level of expression of both IL-1 (facilitates) and IL-6 (blocks), thus influencing the consolidation of learning and memory.

Finally, recent investigations which explored the involvement of IL-1 in neurogenic processes during disease, stress and inflammatory states (Ben Menachem-Zidon et al., 2007; Goshen et al., 2007a; Kaneko et al., 2006; Koo and Duman, 2008; Spulber et al., 2008), have demonstrated that IL-1 can mediate neurogenesis. Although these processes have not been investigated during physiological conditions, there is reason to suggest that this relationship between IL-1 and neurogenesis might, in turn, have an impact on hippocampal-dependent learning and cognitive processes during health (Bruel-Jungerman et al., 2005; Drapeau et al., 2003; Saxe et al., 2007; Shors et al., 2002). Future research should therefore address the relationship between physiological levels of IL-1 and neurogenesis, and how these processes might influence cognitive function.

3.2. IL-6 impacts cognitive function via effects on neurogenesis and synaptic plasticity

Despite evidence to suggest that IL-6 plays an important role in neurodegenerative disease (Harding et al., 2005; Marsland et al., 2006; Rosenberg, 2005; Schram et al., 2007; Weaver et al., 2002; Wright et al., 2006), little is known about the biological actions of IL-6 during health and how these processes influence cognition. This section will therefore concentrate on what is known about the physiological functions of IL-6 within the brain during health; although data on how IL-6 over-expression might affect cognitive function will be briefly discussed. As an introduction to these biological functions of IL-6 in the brain, we briefly outline the synthesis, receptor signalling and signal-transduction pathways of this cytokine.

In the CNS IL-6 is principally synthesized by astrocytes, and to a lesser extent, microglial, and neurons. As with other cytokines IL-6

Table 1
Cognitive-behavioural studies investigating the involvement of cytokines in learning and memory processes.

Study	Species	Animal model	Cytokine	Cognitive-behavioural test	Findings
Yirmiya et al. (2002)	Rat	Long Evans hooded rats (i.c.v. IL-1β, IL-1ra or saline injections)	IL-1	Passive avoidance and Morris water maze	IL-1 plays a critical role in hippocampal-dependent learning and memory processes
Brennan et al. (2003)	Rat	Sprague-Dawley rats (i.p. IL-1β injections – 1, 3, 6 μg/kg or saline)	IL-1	Leverpress avoidance task	Low or moderate doses of IL-1 improved performance on leverpress avoidance task
Depino et al. (2004)	Rat	Wistar rats	IL-1	Inhibitory avoidance task	Endogenous hippocampal IL-1 modulates a fear-motivated learning task; suggesting IL-1 to be apart of hippocampal memory processing
Pugh et al. (2001)	Rat	Rats – induced IL-1 activity (i.c.v. IL-1β, gp120 and i.p. LPS injections and social isolation)	IL-1	Auditory and contextual fear conditioning	Increased IL-1 levels adversely affect hippocampal-dependent memory consolidation processes
Avital et al., 2003	Mouse	wt and IL-1rKO mice 129/Sv × C57BL/6 background	IL-1	Morris water maze and contextual fear conditioning	IL-1 participates in hippocampal-dependent memory processes synaptic plasticity
Goshen et al. (2007a,b)	Mouse	wt and IL-1raTG mice (C57BL/6 × CBA) and wt and IL-1rKO mice (129/Sv × C57BL/6)	IL-1	Morris water maze and contextual fear conditioning	IL-1 exerts a dual role in hippocampal-dependent memory processes; an inverted U-shaped pattern – i.e. the absence and over-expression of IL-1 impairs memory
Braida et al. (2004)	Mouse	wt and IL-6−/− mice CBA × C57BL/6 background	IL-6	Passive avoidance and radial maze	Transgenic IL-1 knockout mice demonstrated improved radial maze and passive avoidance learning
Hryniewicz et al. (2007)	Mouse	wt and IL-6−/− mice C57BL/6 background	IL-6	Novel object recognition task	IL-6 knockout mice displayed impaired recognition memory, suggesting that endogenous IL-6 plays a role in recognition memory
Baune et al. (2008)	Mouse	wt, TNF−/−, TNF R1 and R2 knockout C57BL/6 background	TNF	Barnes maze and novel object recognition task	Absence of TNF has detrimental effects on cognition performance, that is not receptor specific
Fiore et al. (1996)	Mouse	wt and Tg6074 (TNF over-expression) CBA × C57Bl/6 background	TNF	Passive avoidance	Transgenic mice demonstrated altered learning and memory process; a retardation in passive avoidance acquisition
Fiore et al. (2000)	Mouse	wt, Tg6074 and TgK3 (TNF over-expression) CBA × C57BL/6 background	TNF	Passive avoidance and Morris water maze	TNF over-expression in the brain results in disrupted learning capabilities and altered NGF and NPY expression levels
Aloe et al. (1999)	Mouse	wt, Tg6074 and TgK3 (TNF over-expression) CBA × C57BL/6 background	TNF	Morris water maze	Transgenic mice demonstrated memory impairments and altered NGF and BDNF expression levels

exerts multiple physiological functions within the CNS, which are both neuroprotective and neurodegenerative. IL-6 exerts these biological effects through the formation of a hexameric receptor ligand complex (i.e. the binding of IL-6 to IL-6 receptor, which then leads to the homodimerization of gp130, the co-receptor of the IL-6 receptor), which subsequently induces signalling (Ward et al., 1994). The IL-6 receptor, through alternative splicing and shedding, also exists as a soluble form (sIL-6R), which unlike most other soluble cytokine receptors, functions as an agonist. IL-6 mediated responses are, therefore, greatly enhanced by the presence of sIL-6R (Van Wagoner et al., 1999; Van Wagoner and Benveniste, 1999). Moreover, sIL-6R can activate signalling responses in non-IL-6 cells (i.e. cells lacking IL-6 receptors) which express gp130; i.e. through the binding of sIL-6R with gp130. Distinct regions of gp130 activate specific signal-transduction pathways, such as the JAK-STAT, Ras-MAPK and PI-3 kinase (Hirano et al., 1997). Such findings might help explain the redundancy and antagonistic effects seen by cytokine receptors, especially the IL-6 family; although this remains to be clarified.

Recent studies suggest that neurogenesis is important for cognitive function and modulating memory function, such as, memory consolidation and some types of hippocampal-dependent learning (Bruel-Jungerman et al., 2005; Drapeau et al., 2003; Saxe et al., 2007; Shors et al., 2002). Research by Dupret et al. (2007) has, for instance, shown that learning-induced regulation of adult neurogenesis plays an important role in spatial learning, and that dysregulation of hippocampal neurogenesis may underlie age related memory deficits (Drapeau et al., 2003, 2007). Interestingly, IL-6 has been shown to be an important regulator of neurogenesis. As shown by Vallieres et al. (2002), adult transgenic mice which over-express IL-6 by astroglia demonstrated a 63% reduction in neurogenesis in the hippocampal dentate gyrus. Furthermore, research by Monje et al. (2003) has also linked increased IL-6 levels with neural stem cell dysfunction and an associated decline in learning and memory. Such findings demonstrate that the long-term exposure to IL-6, as seen in normal aging (Godbout and Johnson, 2004) and certain neurodegenerative diseases can interfere with cognitive functioning by impairing adult neurogenesis. However, what remains to be clarified is whether basal levels of IL-6 during health participate in cognitive processes.

As investigated by Braida et al. (2004), transgenic mice not expressing IL-6 demonstrated improved cognitive functioning, as indicated by improved radial maze learning and a reduced amnesic effect of scopolamine during passive avoidance testing compared to wild-type mice (see Table 1). In particular, both young and old IL-6 transgenic mice, in comparison to wild-type mice, demonstrated superior and faster acquisition, in terms of both reduced number of working memory errors and shorter time and higher percentage to reach the criterion. On the other hand, research by Hryniewicz et al. (2007), has shown that IL-6 deficiency disrupts object recognition memory, as indicated by less time spent exploring the novel object, which suggests that transgenic IL-6 mice fail to distinguish novel objects from familiar objects (see Table 1). One possible explanation for this discrepancy is that basal levels of IL-6 influence neurogenesis, which in turn mediates some types of hippocampal-dependent forms of learning and memory but not others; although other mechanisms involving choline acetyltransferase (Itzhak and Achat-Mendes, 2004), μ-opioid

receptors, neurodevelopmental anomalies and synaptic plasticity cannot be ruled out (see Braida et al., 2004; Gurwitz, 1997). Despite apparently opposite results, these two experiments do however demonstrate that endogenous IL-6 plays an important role in cognitive function during physiological conditions.

As repeatedly shown, IL-6 also appears to influence synaptic plasticity (Balschun et al., 2004; Jankowsky et al., 2000; Li et al., 1997; Tancredi et al., 2000). As indicated by Li et al. (1997), exogenous IL-6 can suppress the induction of LTP without disrupting previously established LTP. This inhibitory effect of IL-6 on synaptic plasticity has been subsequently shown by Tancredi et al. (2000), to be mediated through mitogen-activated protein kinase ERK (MAPK/ERK). The demonstration that IL-6 is up-regulated following LTP induction (Jankowsky et al., 2000) has provided further evidence that IL-6 may be involved in synaptic plasticity. In support of such findings, Balschun et al. (2004), have shown that neutralizing IL-6 after tetanisation strengthens LTP maintenance. According to the authors, IL-6 appears to play a role in synaptic plasticity opposite to IL-1 and LTP maintenance (Balschun et al., 2004) (see Fig. 1). It has, therefore, been hypothesized that IL-6 under basal conditions may regulate or fine-tune the consolidation of long-term synaptic plasticity and hippocampal-dependent learning by opposing, in a negative-feedback fashion, the effects of IL-1 on LTP maintenance (Balschun et al., 2004) and/or by curtailing synaptic enhancement at neighbouring synapses (Jankowsky et al., 2000). Further research is needed to elucidate the role in which IL-6 plays in synaptic plasticity, neurogenesis and cognitive function, during health and pathological conditions in which increased levels of IL-6 have been implicated.

3.3. TNF alpha influences cognitive function through direct effects on LTP and synaptic scaling

Tumor necrosis factor is a pro-inflammatory cytokine which has been shown to exert physiological, neuroprotective (Cheng et al., 1994; Gemma et al., 2007; Pan and Kastin, 2001; Schwartz et al., 1994) and neurodegenerative (Perry et al., 2001) effects within the nervous system. These pleiotropic effects are exerted by TNF via activation of two receptors, TNF-p55 receptor and TNF-p75 receptor. Often referred to as TNF-R1 and TNF-R2 respectively, these two distinct receptors have been shown to elicit different molecular and cellular responses (Baud and Karin, 2001; Chen and Goeddel, 2002; MacEwan, 2002a,b; Wajant et al., 2003). For instance, TNF-R1 has been shown to initiate the activation of caspases and ultimately apoptosis (MacEwan, 2002a,b). This 'death-signalling' intracellular pathway appears to be activated by a specific cytoplasmic domain identified in TNF-R1, referred to as the 'death domain'. TNF-R2 lacks this 'death domain' and appears to inhibit the activation of caspases and protect against apoptosis; albeit there is some evidence to suggest that TNF-R2 activation can induce cell death (see Wajant et al., 2003 for further details).

Recent research shows considerable advancement in the understanding of TNF bioactivity within the CNS. For example, TNF has the biological property to act as a neuromodulator within the brain (Blatteis, 1990; Szelenyi, 2001; Vitkovic et al., 2000a,b). Moreover, TNF has been shown to play a role in both glutamate excitotoxicity (i.e. by inhibiting glutamate transporters on astrocytes) and glutamate transmission (see Pickering et al., 2005 for a review). More specifically, Beattie et al. (2002) demonstrated that glial-derived TNF markedly influenced synaptic efficacy by up-regulating surface expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) receptors. In support of these findings, it was established subsequently by Stellwagen et al. (2005) that the up-regulation of AMPA receptors by TNF is mediated through TNF-R1 and phosphatidylinositol 3 (PI3) kinase-dependent processes. Interestingly, it was also determined by these researchers, that TNF simultaneously causes a decrease in synaptic inhibition via endocytosis of $GABA_A$ receptors (Stellwagen et al., 2005). Such findings support a neuromodulatory role for TNF within the brain and suggest a possible role for TNF in synaptic plasticity.

The stability and cycling of AMPA receptors at synapses has been shown to be an essential process in both LTP and LTD (Malenka and Bear, 2004; Malenka and Nicoll, 1999). Since TNF-α has been shown to up-regulate AMPA receptors (Beattie et al., 2002; Stellwagen et al., 2005) it has been postulated that TNF might serve an essential function in Hebbian synaptic plasticity and possibly learning and memory. Research by Tancredi et al. (1992) and Cunningham et al. (1996), but not others (i.e. Stellwagen and Malenka, 2006) have demonstrated that patho-physiological levels of TNF inhibit LTP in the dentate gyrus of rat hippocampal slices. In support of these findings, Butler et al. (2004) determined that the inhibitory effect of TNF on LTP is a biphasic response. More specifically, their research demonstrated that the inhibition of early phase LTP by TNF is dependent on a p38 mitogen-activated protein kinase process, whereas, late phase LTP inhibition is p38 MAPK-independent (Butler et al., 2004). Subsequent research (i.e. Cumiskey et al., 2007) has further shown that TNF inhibition of LTP is dependent on TNF-R1 and mGlu5-receptor activation. In addition to these findings, Albensi and Mattson (2000) have demonstrated a role for endogenous TNF and NF-κB signalling in LTD induction. Unlike the exogenous studies previously mentioned, the results from Albensi and Mattson (2000) provide evidence for a TNF-mediated physiological role in synaptic plasticity.

Although these results support a role for TNF in LTP and LTD, alternative suggestions have been made (Stellwagen and Malenka, 2006). In a series of elegant experiments, Stellwagen and Malenka (2006) demonstrated that endogenous glial-derived TNF is critical for homeostatic synaptic scaling. In particular, it was shown that during prolonged inactivity TNF shifts neurons towards more excitation and less inhibition (Stellwagen and Malenka, 2006) (see Fig. 2). Such findings support recent studies that glial cells play an essential role in neuronal processing, synaptic integration and synaptogenesis (Bains and Oliet, 2007; Bezzi and Volterra, 2001; Halassa et al., 2007a; Slezak and Pfrieger, 2003; Turrigiano, 2006; Vesce et al., 2001). Although poorly understood, glial modulation of neuronal activity appears to involve cytokines such as TNF and BDNF (see Halassa et al., 2007b; Rutherford et al., 1998; Swanwick et al., 2006; Volterra et al., 2002 for details). Moreover, there is now reason to believe that glial–neuronal homeostatic synaptic plasticity mediated by TNF plays an essential role in learning and memory (Bains and Oliet, 2007; Turrigiano, 2006, 2007). The clarification of TNF's participation in synaptic plasticity is not only warranted, but might otherwise explain cognitive-behavioural findings (see Table 1 for details) that disruption of these physiological processes leads to cognitive impairment.

As recently shown by this research group the presence of TNF, in mice, under immunologically non-challenged conditions is essential for normal functions of memory and learning (Baune et al., 2008). Cognitive impairment has also been demonstrated in transgenic mice over-expressing TNF (Aloe et al., 1999; Campbell et al., 1997; Fiore et al., 1996, 2000). This TNF over-expression-associated decline in cognitive function might relate to changes in synaptic plasticity (Small, 2008; Tobinick and Gross, 2008a) and/or possibly decreased NGF levels (Fiore et al., 2000); which has been shown to impair long-term potentiation (Kelly et al., 1998, 2000) and cause neurodegeneration (Capsoni and Cattaneo, 2006; Capsoni et al., 2000, 2002). Future research is, therefore, needed

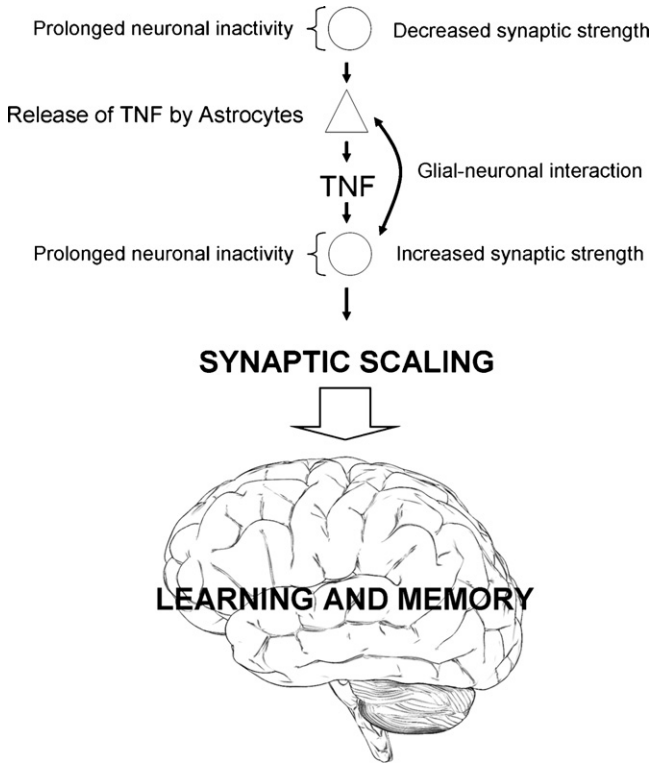

Fig. 2. Schematic illustration of the involvement of TNF in synaptic scaling a non-Hebbian form of synaptic plasticity. In brief, a prolonged period of neuronal inactivity leads to a decrease in synaptic strength, which triggers, via glial–neuronal communication, the release of TNF by astrocytes. In a reciprocal fashion, the released TNF by astrocytes influences the activity of the post-synaptic neuron resulting in an increase in synaptic strength. Collectively, this helps to maintain neuronal activity 'synaptic scaling' and learning and memory functions.

to unravel the participation of TNF in synaptic plasticity and cognitive function during health and disease.

3.4. Other potential mechanisms by which cytokines might mediate cognitive processes

Based on the pleiotrophic biological properties of cytokines, it is plausible that cytokines might influence synaptic plasticity and/or cognitive processes via alternative mechanisms then those stated above (see Fig. 3 for schematic illustration). For instance, pro-inflammatory cytokines, such as IL-1 and TNF have been shown to activate small G-proteins such as, Ras, Rho, Rac and Rap1 (MacEwan, 2002a,b; Williams et al., 2008). Of particular interest in regards to cytokine-mediated cognition is recent evidence that glia-derived TNF inhibits neurite outgrowth and branching by activating RhoA in neurons (Neumann et al., 2002). Since synaptogenesis and dendritic branching serve an essential role in synaptic plasticity and learning and memory processes (Muller et al., 2000, 2002; Remy and Spruston, 2007), TNF might exert profound effects on cognitive functioning through such mechanisms. Although this has not be well studied, recent evidence has implicated Rho in mental retardation, synaptic plasticity (i.e. synaptogenesis and dendritic branching) and cognition (Chechlacz and Gleeson, 2003; Govek et al., 2005; Meng et al., 2005; Newey et al., 2005; Ramakers, 2002). Future research is, therefore, needed to clarify the role in which cytokines, such as TNF, might play in synaptogenesis, dendritic branching and how these processes might relate to Rho activation and cognitive processes.

Other evidence has suggested that P2x7 receptors (P2 purinergic receptors) serve an important role in neuronal–glia communication and cytokine-mediated processes within the brain (Bennett, 2007; Lister et al., 2007; Sperlagh et al., 2006). Purinergic receptors are divided into two major families, which bind adenosine (P1 receptors), and ATP, ADP, UTP or UDP (P2 receptors). P2 purinergic receptors are further divided into ligand-gated channel or ionotropic receptors (P2X receptors) and G-protein coupled receptors (P2Y receptors). In particular, P2x7 has been recognized as an important receptor for several inflammatory molecules, such as IL-1, IL-6 and TNF. In particular, it is believed that P2x7 receptors play a key role in the brain cytokine response to immune stimuli that leads to sickness behaviour and possibly depression and/or cognitive dysfunction (Bennett, 2007; Mingam et al., 2008). Future research should also be directed at elucidating such possible mechanisms and pathways in both disease and health.

3.5. Other cytokines potentially influencing cognitive function

3.5.1. Alpha1-antichymotrypsin (ACT)

Biochemical and genetic studies indicate that ACT is important in the pathogenesis of Alzheimer's disease. In a study using several lines of transgenic/knockout mice it was shown that human ACT separately and synergistically with ApoE facilitate both diffuse A beta immunoreactive and fibrillar amyloid deposition, thus promoting cognitive impairment in aged PDAPP(V717F) mice. The degree of cognitive impairment was correlated with the ApoE- and ACT-dependent hippocampal amyloid burden (Nilsson et al., 2004). Further supportive data for the involvement of ACT in cognitive decline stems from a population-based study showing that the serum inflammatory protein alpha1-antichymotrypsin was associated with cognitive decline in older persons (Dik et al., 2005).

In a clinical genetic study among patients with a clinical diagnosis of probable AD and patients with early onset AD, the ACT gene appeared to influence the early clinical development of the disease and the interaction of the ACT and ApoE genes affected clinical progression of AD (Licastro et al., 2005). Interestingly, in a study among 108 patients with late onset AD, the authors report an association between the ACT polymorphisms but they failed to show an association between ACT serum levels and ACT polymorphism as well as a correlation between ACT serum levels and cognitive function (McIlroy et al., 2000).

In summary, the data suggest consistent genetic findings of ACT polymorphism effects on cognitive function in AD in human which is in line with results from some animal studies; however no information is available to date on the direct involvement of ACT in molecular mechanisms of learning and memory.

3.6. Interferon-gamma (IFN-gamma)

In a recent animal study it was demonstrated that the cytokine IFN-gamma enhances neurogenesis in the dentate gyrus of adult mice and improves the spatial learning and memory performance of the animals (Baron et al., 2008). In older mice, the effect of IFN-gamma is more pronounced in both wild-type mice and mice with Alzheimer's-like disease and is associated with neuroprotection (Baron et al., 2008). The authors suggest that limited amounts of IFN-gamma in the brain shape the neuropoietic milieu to enhance neurogenesis, possibly representing the normal function of the immune system in controlling brain inflammation and repair (Baron et al., 2008).

It is well known that cell renewal in the adult central nervous system is limited, and is blocked under inflammatory brain conditions. In an animal study it was demonstrated that neurogenesis of adult neural progenitor cells in mice are blocked by inflammation-associated microglia. Microglia activation occurred

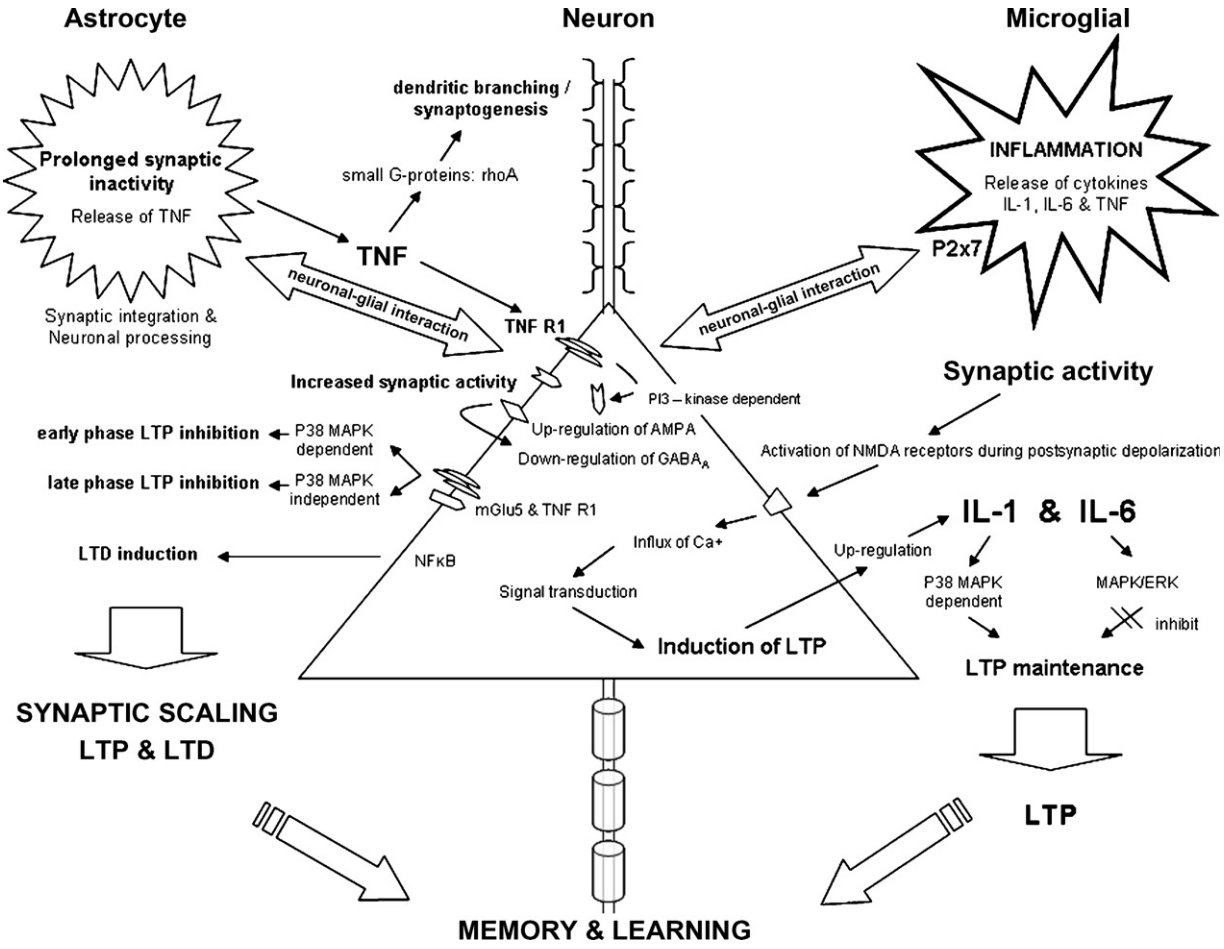

Fig. 3. Schematic representation of the key cytokine-mediated molecular mechanisms and neuronal–glial interactions that subserve synaptic plasticity and learning and memory processes in the brain. During pathological conditions microglial interact with neurons, possibly via P2x7 receptors, to induce a neuroinflammatory response characterized by an up-regulation of cytokines, such as, IL-1, IL-6 and TNF, which can then alter the normal balance and physiological function of cytokines in synaptic plasticity. Alternatively, during normal physiological conditions astrocytes play a central role in synaptic integration and neuronal processing. In particular, the release of TNF from astrocytes (often due to prolonged synaptic inactivity) results in the activation of several different downstream processes, such as (1) activation of small G proteins (rhoA) which can have profound effects on dendritic branching and synaptogenesis, (2) up-regulation of AMPA receptors via activation of TNF receptor 1 (TNF-R1) and PI3 kinases, with the resultant rise in AMPA receptors leading to an increase in synaptic activity, (3) activation of TNF-R1 and metabotropic glutamate receptor 5 (mGlu5) leading to either early phase long-term potentiation (LTP) inhibition (via p38 MAPK dependent activity) or late phase LTP inhibition (via p38 MAPK independent activity) and (4) the activation of transcription factor NF-κB resulting in the induction of long-term depression (LTD). Alternatively, normal synaptic activity can lead to the activation of NMDA receptors during post-synaptic depolarization which then leads to an influx of intracellular calcium (Ca+) and further signal transduction. Collectively these processes lead to the induction of LTP and the up-regulation of IL-1 and IL-6. IL-1 and IL-6 exert, via similar downstream mechanisms, opposing effects on the maintenance of LTP, which works in a negative-feedback fashion to fine-tune the consolidation of long-term synaptic plasticity. Collectively all these processes can influence LTP, LTD, synaptic scaling and possibly other cellular mechanisms that subserve learning and memory.

through low level of IFN-gamma (Butovsky et al., 2006). Thus, it is suggested that IFN-gamma has the potential to stimulate neurogenesis, and the possibility to play a role in development and repair of the CNS (Kim et al., 2007). Moreover, since IFN-gamma is able to stimulate neurogenesis, a potential neural correlate of memory consolidation, it can be hypothesized that IFN-gamma has the potential ability to directly or indirectly subserve memory consolidation; however testing of this hypothesis is still outstanding.

Finally, clinical reports suggest that interferon (IFN) therapy is associated with neuropsychiatric side-effects including cognitive dysfunction and mood syndromes with varying rates of IFN-induced depression approaching up to 50% in recent studies (Valentine and Meyers, 2005).

3.7. Interleukin-2 (IL-2)

Relatively little direct evidence for the involvement of IL-2 in cognitive function is available to date. In a clinical study conducted among cancer patients, subcutaneous IL-2 was shown to impair spatial working memory and lower accuracy of planning abilities. In contrast, patients treated with IFN-alpha did not show any impairment in performance accuracy in these tasks but showed longer latencies in reaction time. Most of these early alterations persisted at the end of the first month of treatment without any obvious sign of worsening (Capuron et al., 2001).

The neurotoxic effects of IL-2 in the above human study are supported by findings from animal research which showed that IL-2 gene deletion alters the neuroimmunological status of the mouse hippocampus through a dysregulation of cytokines produced by CNS cells associated with increased hippocampal neurogenesis in male mice (Beck et al., 2005b).

3.8. Cytokine signalling pathways in the injured brain

Only limited evidence on the manipulations of the cytokines induced effects on cognition through pharmacological interventions has emerged over the past 10 years. In an experimental study, the effect of systemic administration of human recombinant

interleukin-1 receptor antagonist (rhIL-1ra) on behavioral outcome was evaluated after brain injury in Sprague-Dawley rats (Sanderson et al., 1999). Postinjury administered high-dose rhIL-1ra significantly attenuated posttraumatic neuronal loss in the injured hippocampal CA3 region, dentate hilus, and cortex but impaired recovery of motor function at 7 days after trauma. In addition, postinjury administration of rhIL-1ra significantly attenuated cognitive deficits. These results suggest that inhibitors of cytokine pathways may be therapeutically useful for the treatment of brain trauma. Applying a similar animal study design this time using monoclonal antibodies (mAB), it was found that the treatment with either TNF- or IL-6-mAB had no effect on neurological motor, cognitive function or brain edema during the first post-injury week (Marklund et al., 2005). Studies using other than vascular models of cognition show that anti-TNF treatment of humans with Alzheimer's disease may lead to rapid cognitive improvement. However, it is unclear from this human study which TNF receptor mediated the improvement (Tobinick, 2007; Tobinick et al., 2006; Tobinick and Gross, 2008b).

Antagonistic effects of celecoxib, a selective cycloxygenase-2 (COX-2) inhibitor, on age-dependent increased cytokine expressions of IL-1beta and TNF in the hippocampus in the aging rat were investigated (Casolini et al., 2002). Since the chronic oral treatment with celecoxib was able to contrast the age-dependent increase in hippocampal levels of pro-inflammatory markers and circulating anti-inflammatory corticosterone (provided that intervention started at an early stage of aging), the results suggest a preventive potential of COX-2 inhibitors. However, it is still speculative that age-related impairments in cognitive ability may be ameliorated as cognition-like behaviour was not assessed in this animal study (Casolini et al., 2002).

Cytokine effects can also interact with receptors of other brain systems mediating disease states such as pain. In an animal study investigating the role of peripheral groups I and II metabotropic glutamate receptors (mGluRs) in interleukin-1beta (IL-1beta)-induced mechanical allodynia in the orofacial area, it was found that the peripheral group I mGluR antagonists blocked the IL-1beta-induced mechanical allodynia, while peripheral group II mGluR agonists produced anti-allodynic effects on IL-1beta-induced mechanical allodynia in the orofacial area of rats (Ahn et al., 2005).

The limited studies to date on cytokine receptor involvement in cognitive function in humans and animal models indicate the need for further research covering a larger range of cytokines as well as inflammatory diseases to enhance the understanding of the underlying mechanisms, but also with the aim to translate the research into clinical pharmacological applications for the treatment of neuropsychiatric diseases characterized by cognitive impairment such as dementia and depression.

4. Limitations and future research

The research on cytokine involvement with cognitive function and cognitive impairment leading to the proposed cytokine model of cognitive function is largely based on animal studies as well as clinical studies in humans as evaluated in this review. While animal studies help to understand the molecular and cellular mechanisms of learning and memory and cognitive function, clinical studies contribute to the understanding of cognitive impairment in humans with circumscribed diseases such as dementia. The major limitations of the research on this topic are the relatively few cytokines for which sufficient evidence of their molecular and cellular effects related to cognitive function and/or learning and memory is readily available and secondly the largely missing link of translational research from basic science to clinical applications. This is evidenced by the few published studies in humans applying the principle of cytokine blockade in order to improve cognitive performance as demonstrated with anti-TNF treatment in dementia (Tobinick et al., 2006).

The research on cytokines in cognitive function in humans is also limited by the difficulty to make use of pharmacological receptor blockade of cytokine effects involved in cognitive function. The development of receptor specific antibodies for the use in humans without causing significant side-effects and the translation from animal research would hold potential for the development of new treatments for various neuropsychiatric conditions related with cognitive decline. Finally, the translation of animal research assessing cognition-like behaviour to more complex human behaviour is a challenge in itself. Although the animal models provide reliable and valid cognitive measures, neurospychological concepts in humans such as word fluency, executive function and consciousness are difficult to capture or represent in animal models. However, future research on cytokines in cognitive function would benefit from an approach in which line of evidence for cytokine effects on cognitive function is created including animal models and clinical applications covering molecular cellular and clinical studies.

5. Clinical implications and conclusions

There is now considerable evidence to suggest that cytokines mediate essential nervous system functions during health that lie outside their functions in traditional immune and inflammatory processes (Bauer et al., 2007; Pickering and O'Connor, 2007; Vitkovic et al., 2000a; Viviani et al., 2007). In particular, data suggests that pro-inflammatory cytokines, such as IL-1, IL-6 and TNF, serve a specific function in synaptic plasticity and cognitive processes. Additional evidence is seen for effects of ACT and IFG-gamma on cognitive function. Further clarification and future inclusion of other potential candidates of the suggested cytokine-mediated model of cognition will not only provide better understanding of these physiological processes, but might also have direct relevance to the understanding of pathological changes seen in certain neuropsychiatric diseases. For instance, as suggested by Small (2004, 2008), the progression of Alzheimer's disease might be driven by exaggerated, TNF-mediated, synaptic scaling during prolonged inactivity caused by β-amyloid. It must be emphasized here, that it is the physiological function of TNF in synaptic scaling (i.e. thought to subserve cognitive processes) and not inflammatory or pathophysiological processes of TNF that is postulated to be driving disease progression. Although it remains to be clarified, clinical data obtained by Tobinick (2007), Tobinick et al. (2006) and Tobinick and Gross (2008a) suggests that the rapid cognitive improvement seen in Alzheimer's disease patients receiving anti-TNF treatment (i.e. perispinal administration of etanercept) maybe the result of reversed excess TNF-mediated synaptic plasticity dysregulation. Future research aimed at elucidating the role in which TNF plays in normal synaptic plasticity might lead to better disease understanding and therapeutic intervention.

Depression might also represent an exaggerated form of cytokine-mediated behaviour, in that cytokines naturally exert a normal role in the brain that manifests as 'sickness behaviour' in disease models with over-expressed cytokines (Dantzer et al., 2008). This natural behavioural change is both adaptive and physiological, but during prolonged inflammation and/or psychological stress might lead to the pathogenesis of depression. The 'hijacking' of these physiological processes during disease might also explain the high comorbidity between neurodegenerative diseases and depression (Caballero et al., 2006) and why depression is a risk factor for neurodegenerative diseases (McDonald et al., 2003; Ownby et al., 2006). The clinical application of anti-inflammatory treatments

in depression is still outstanding, although the present basic science data are suggestive of such a translation research approach.

Finally, the clarification and understanding of the physiological functions of cytokines within the brain might also provide insight into age-associated cognitive decline (Bodles and Barger, 2004; Griffin et al., 2006; Lynch, 1998; Maher et al., 2005; Nolan et al., 2005).

In summary, the review provides evidence that cytokines mediate essential nervous system functions during health that lie outside their functions in traditional immune and inflammatory processes. In particular, the cytokines IL-1eta, IL-6 and TNF-alpha hold biological features at the molecular level, such as synaptic plasticity, neurogenesis and neuromodulation, and at cellular mechanisms subserving learning, memory and cognition under physiological conditions. These cytokine-mediated cognitive processes have significant implications in healthy states as well as in the long-term development and pathogenesis of specific neuropsychiatric disorders such as major depression and dementia.

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