

# Cytokines and Cognition—The Case for A Head-to-Toe Inflammatory Paradigm

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The brain is not only immunologically active of its own accord, but also has complex peripheral immune interactions. Given the central role of cytokines in neuroimmunoenocrine processes, it is hypothesized that these molecules influence cognition via diverse mechanisms. Peripheral cytokines penetrate the blood-brain barrier directly via active transport mechanisms or indirectly via vagal nerve stimulation. Peripheral administration of certain cytokines as biological response modifiers produces adverse cognitive effects in animals and humans. There is abundant evidence that inflammatory mechanisms within the central nervous system (CNS) contribute to cognitive impairment via cytokine-mediated interactions between neurons and glial cells. Cytokines mediate cellular mechanisms subserving cognition (e.g., cholinergic and dopaminergic pathways) and can modulate neuronal and glial cell function to facilitate neuronal regeneration or neurodegeneration. As such, there is a growing appreciation of the role of cytokine-mediated inflammatory processes in neurodegenerative diseases such as Alzheimer's disease and vascular dementia. Consistent with their involvement as mediators of bidirectional communication between the CNS and the peripheral immune system, cytokines play a key role in the hypothalamic-pituitary-adrenal axis activation seen in stress and depression. In addition, complex cognitive systems such as those that underlie religious beliefs, can modulate the effects of stress on the immune system. Indirect means by which peripheral or central cytokine dysregulation could affect cognition include impaired sleep regulation, micronutrient deficiency induced by appetite suppression, and an array of endocrine interactions. Given the multiple levels at which cytokines are capable of influencing cogni-

tion it is plausible that peripheral cytokine dysregulation with advancing age interacts with cognitive aging.

**Key words:** cytokines; cognition; Alzheimer's disease; inflammation

**B**ecause of the blood-brain barrier (BBB), which selectively filters bloodborne cells and proteins, the brain has often been viewed as a sequestered organ, protected and isolated from the rest of the body, but the brain is now seen as an immunologically active organ in direct communication with the immune and endocrine systems. The immune system is a striking example of the integrated connections between the brain and the body. Thus, systemic inflammatory reactions and responses can influence brain function. Conversely, central nervous system (CNS) processes may affect distant organs. Central to the fields of neuroscience and immunology is the field of cytokine biology. An emerging concept as yet not fully explored is the potential for cytokines, in their role as peripheral inflammatory mediators, to directly or indirectly affect cognition. In this review, we explore the brain-body connection mediated by the cytokine network and its effect on cognitive function, with the understanding that cognitive impairment may stem from multiple etiologic mechanisms that affect biological and psychological functioning.

## CYTOKINES—CATEGORIZATION AND PHYSIOLOGY

Cytokines are nonantibody proteins that can be made by a wide range of cell types. About 30 cytokines are recognized, including the interleukins (IL-1 to IL-24), tumor necrosis factors (TNFs), and transforming growth factors (TGF Beta 1–3). In general, cytokines are low molecular weight (<200 amino acids) and have specific receptors. Collectively, cytokines mediate cellular intercommunications via autocrine, paracrine, or endocrine mechanisms. Cytokine actions are the result of a complex network, often involving feedback loops and cascades, the overall response being dependent on the synergistic or antagonistic actions of its various components. As a result of their pleiotropism, it is difficult to pinpoint the specific actions

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of individual cytokines. The specificity of the cytokine response is determined by unique cytokine cell membrane receptors. In addition, soluble cytokine receptors may inhibit a specific cytokine's activity by preventing it from binding to cell membrane receptors, for example, as demonstrated with TNF.<sup>1</sup> Less commonly, soluble receptors serve to augment the cytokine response, for example, in the case of the soluble IL-6 receptor.<sup>2</sup> At least in the periphery, IL-1, IL-6, and TNF $\alpha$  are typically considered proinflammatory, whereas IL-4, IL-10, and IL-13 are typically considered antiinflammatory,<sup>3</sup> the conditionality of which is dependent upon the immediate environment.

Over the last decade, transgenic mouse models have facilitated a multilevel analysis of pathologic, electrophysiological, neuroendocrinological, and behavioral effects of cytokine over- or underproduction. To determine the effects of central cytokine overexpression, cytokine coding sequences are inserted into a CNS-specific gene promoter construct, the glial fibrillary acidic protein (GFAP) vector, which targets expression in astrocytes.<sup>4</sup> Transgenic lines have been developed for multiple cytokines, including IL-3, IL-6, IL-12, interferon-alpha (IFN- $\alpha$ ), interferon-gamma (IFN- $\gamma$ ), TGF- $\beta$ , and TNF- $\alpha$ , with each transgenic overexpression or knock-out model theoretically manifesting its cytokine's distinct actions.

#### AGE-RELATED PERIPHERAL CYTOKINE DYSREGULATION AND COGNITION

A general decline in immunological functioning is considered a hallmark of the aging process. Increasing age has been associated with changes in serum levels of various cytokines, although quantitative cytokine changes in healthy older people have not been uniformly demonstrated.<sup>5</sup> Serum IL-6 increases with advancing age in various healthy populations have been widely reported.<sup>6-9</sup> As such, it appears that increases in IL-6 represent a usual outcome of aging, independent of comorbid disease processes. The age-associated rise in IL-6 may play a role in thymic atrophy and the suppression of thymopoiesis during aging.<sup>10</sup> In addition, age-related increases in TNF- $\alpha$  and TNF receptors have been demonstrated in blood, whereas negative findings have been found when mononuclear cells were studied.<sup>1,11</sup>

The cause of this age-related cytokine dysregulation is unclear and could include normal homeostatic responses and disease processes. One possible mechanism is suggested by findings that dehydroepiandrosterone (DHEA) inhibits IL-6 secretion from human mononuclear cells *in vitro*. Thus, an age-related increase in IL-6 could be due to a loss of tonic inhibition by DHEA as levels of this adrenal hormone decrease with advancing age.<sup>12</sup> Advanced glycation end products (AGEs), reactive derivatives of nonenzymatic glucose macromolecule products that accumulate in human tissues with age, are implicated by way of induction of proinflammatory cytokine expression through nuclear factor- $\kappa$ B (NF- $\kappa$ B) transcription factor-dependent pathways.<sup>13</sup>

The paradigm of an immune dysregulation involving cytokines has been recently applied to the concept of frailty. Cross-sectional studies have identified an association between increases in IL-6 and functional status as indicated by activity of daily living (ADL) or instrumental activity of daily living (IADL) measures<sup>14</sup> and with mortal-

ity.<sup>15</sup> These analyses controlled for comorbid illnesses. IL-6 levels are also longitudinally correlated with subsequent development of disability in ADLs/IADLs and subsequent mortality.<sup>16</sup> In addition, elevated levels of TNF- $\alpha$  are associated with increased mortality risk in older institutionalized patients.<sup>17</sup>

Given that the performance of certain of these ADLs/IADLs require cognitive processing,<sup>18</sup> and, given that inflammatory processes underlie or mediate the progression of many neurodegenerative processes, it is possible that an age-associated peripheral cytokine dysregulation, and perhaps a central age-associated cytokine dysregulation, may influence cognition. In support of such a hypothesis, a recent prospective cohort study by Weaver et al.<sup>19</sup> from the MacArthur Foundation Program in Successful Aging showed that high levels of serum IL-6 are correlated with lower cognitive functioning in cross-sectional analysis, but also predict subsequent cognitive decline. If confirmed, it remains to be determined whether such cytokine levels represent "spillover" from CNS inflammatory processes or an influence of peripheral cytokine dysregulation on cognitive processing.

Although peripheral overexpression of IL-6<sup>20</sup> or TGF- $\beta$ 1<sup>21</sup> by transgenic mice does not produce neurodegeneration, it is possible that actions of other cytokines, which become up- or downregulated in response, compensate for the effects of overproduction of a single cytokine. In addition, one must consider that cognitive impairment does not necessarily equal neurodegeneration; thus peripheral cytokines can still influence neurotransmission and cause cognitive deficits via effects on sleep and nutritional intake, for example, without causing neuronal death. Evidence supporting the influence of peripheral cytokine dysregulation on cognition has come from the use of cytokines as therapeutic agents. Psychiatrically normal individuals who receive systemic cytokines such as IFN- $\alpha$ , IL-2, and TNF- $\alpha$  at therapeutic doses frequently describe increased somatic complaints, anorexia, and neuropsychiatric side effects, including depressed mood, disordered sleep, poor motivation, and impaired thought processing.<sup>22</sup>

#### MECHANISMS OF CYTOKINE ENTRY INTO THE CNS

Although the primary mode of peripheral cytokine entry into the CNS remains undetermined, there is substantial evidence that peripheral cytokines are capable of effecting central neurophysiologic changes. One line of evidence relates to "sickness behavior," a syndrome seen during the initial phase of infection or during acute flares of a chronic disease involving immune system activation. The manifestations of sickness behavior include fever, lethargy, increased sleep, reduced social activity, reduced mobility, anhedonia, decreased learning, anorexia, and decreased libido.<sup>23,24</sup> Sickness behavior can be brought on by endotoxins (e.g., lipopolysaccharides (LPSs)) or by cytokines (e.g., IL-1). LPSs stimulate macrophages to produce IL-1, IL-6, and TNF- $\alpha$ ; thus, peripheral cytokines most likely mediate LPS-induced effects.<sup>25</sup> In keeping with this hypothesis, blockade of the IL-1 $\beta$  receptor with IL-1 receptor antagonist (IL-1ra) has been shown to prevent the onset of the

sickness response to LPS.<sup>26</sup> Concomitant with the sickness behavior response to peripheral agents are regionally specific increases in brain norepinephrine, serotonin, tryptophan, and dopamine metabolism in mice.<sup>27</sup>

How can peripheral cytokines effect a central behavioral response? Active transport mechanisms have been documented for IL-1,<sup>27</sup> TNF,<sup>28</sup> and IL-1ra<sup>29</sup> as has direct entry at circumventricular regions (e.g., the organum vasculosum lateralis terminalis (OVLT)) where the BBB is less stringent.<sup>30</sup> In addition, binding of cytokines to endothelial receptors in the brain vasculature with subsequent release of other mediators (e.g., endothelial cell adhesion molecules, chemokines, nitric oxide and prostaglandins) leads to impairment of BBB integrity.<sup>31,32</sup> Activated T cells that have crossed the BBB, dependent on molecules such as P-selectin,<sup>33</sup> represent another potential source of CNS cytokine exposure.

An alternative hypothesis, proposed by Dantzer et al.,<sup>26</sup> is that afferent neurons are directly responsive to peripheral cytokine stimulation, the signal then being transmitted to the CNS where it activates the centrally mediated aspects of sickness behavior. IL-1 receptor messenger ribonucleic acid (mRNA) has been detected in vagal afferent neuronal cell bodies.<sup>34</sup> More recently, direct stimulation of vagal sensory nerve activity by IL-1 has been demonstrated.<sup>35</sup>

The nucleus tractus solitarius (NTS), the site of termination of the vagus nerve in the brainstem, shows intense activation after peripheral administration of LPS or IL-1 $\beta$  at doses that do not induce uptake at the OVLT.<sup>30</sup> The NTS has connections to the preoptic area of the anterior hypothalamus responsible for fever regulation, suggesting a pathway for the pyrogenic effects of IL-1. Subdiaphragmatic vagotomy has been shown to block fever after peripheral LPS administration,<sup>36</sup> further supporting the role of the vagus nerve in mediating central effects of peripheral cytokines. Vagotomy has also been shown to block the depressant effects of peripherally administered LPS on social exploration and food-motivated behavior in animal studies.<sup>37</sup> Perhaps most definitively, peripheral administration of IL-1 $\beta$  and LPS has been shown to induce brainstem and hippocampal IL-1 $\beta$  production and central expression of IL-1, IL-6, and TNF- $\alpha$  mRNA effects that are blocked by vagotomy.<sup>38,39</sup>

It thus appears that cytokine stimulation of peripheral sensory neural afferents leads to central cytokine production or central alterations in neurotransmission. The vagus nerve plays a central role in cytokine signal transmission and resultant centrally mediated physiological and cognitive-behavioral manifestations of sickness behavior.

### CYTOKINES AND NEUROPHYSIOLOGY

A highly regulated network of cytokines and soluble cytokine receptors modulates neuronal and glial cell function.<sup>40,41</sup> In part, this relates to their ability to influence neurotransmission. Both systemic and central cytokine administration can cause increases in noradrenergic, dopaminergic, and serotonergic metabolism in the hypothalamus,<sup>42,43</sup> hippocampus,<sup>44</sup> and nucleus accumbens.<sup>45</sup>

A number of investigators have suggested constitutive expression of various cytokines and cytokine receptors in the normal human brain in the absence of a pathologic

stimulus (Table 1). Although relative degrees of expression in neurons, astrocytes, and microglia vary, there also appears to be some spatial variation with respect to cytokine secretion. In rodent brain tissue, for example, the highest densities of receptors for IL-1, IL-2, IL-6, and TNF- $\alpha$  have been localized in the hippocampus and hypothalamus.<sup>41</sup>

It appears that CNS levels of certain cytokines increase as a function of age. Neurologically intact patients show a progressive increase in brain expression of IL-1 and microglial activation with age.<sup>46</sup> Increases in brain IL-6 levels in the mouse brain have been found with advancing age, probably as a result of increased microglial production.<sup>47</sup> Older rats show no defects in their ability to produce a behavioral, functional, or cytokine response to brain administration of IL-1 $\beta$ .<sup>48</sup> An intact CNS response to age-associated cytokine elevations might result in an increased risk of cytokine-driven neurodegenerative responses.

Recent analyses of mRNA by microarray technology in aging brains have yielded interesting results.<sup>49,50</sup> The majority of mRNA changes, found primarily in the cerebellum and cortex, are increases of sequences associated with inflammation. Several of these mRNAs that change in aging mice increase the glial activation marker GFAP in astrocytes and complement C1q in microglia. Caloric restriction, which slows aging processes in rodents, attenuate many of these age-related changes in mRNA.<sup>51-53</sup> The downregulation of inflammatory gene expression is consistent with the ability of caloric restriction to decrease peripheral inflammatory responses.<sup>53,54</sup>

Although much research has targeted the role of glial cells in CNS inflammatory mechanisms, the functions of cytokines extend beyond that paradigm to encompass neuromodulatory roles in CNS development and repair. IL-1, IL-6, and TNF- $\alpha$  show trophic effects on developing neurons and glia,<sup>55</sup> and IFN- $\gamma$  promotes neuronal differentiation.<sup>56</sup> IL-1 may also be involved in modulating the synaptic plasticity underlying learning and memory in the developing brain.<sup>55</sup> In many respects, neuronal repair mechanisms involving cytokines mirror those in operation during neuronal development.<sup>56</sup> IL-6 enhances survival of catecholaminergic neurons in rats<sup>57</sup> and promotes reactive gliosis in transgenic mouse models.<sup>56</sup> Dysregulation of these repair mechanisms, for example, in the presence of a pathological stimulus such as increased soluble or fibrillar aggregates of amyloid- $\beta$  or oxidative stress, could promote neurodegeneration.

### CYTOKINES AND CNS INFLAMMATION

As mediators of inflammatory processes, cytokines are known to produce toxic effects peripherally. Their production has been shown to be centrally upregulated in regions undergoing neurodegeneration or, in the case of Alzheimer's disease (AD), in regions manifesting amyloid- $\beta$  (Ab) deposits or neurofibrillary tangles. Because cytokines are involved in neurodevelopmental processes, brain injury repair mechanisms, inflammation, and autoimmune processes, dysregulation of cytokine systems may be a common response to a range of pathophysiological insults. Once the inflammatory cascade has been stimulated, cytokines can amplify their own production via autocrine induction or interact with other inflammatory mediators,

Table 1. Summary of Peripheral and Central Cytokine Actions

	IL-1	IL-2	IL-6	TNF-alpha	TGF-beta	Interferons
Peripheral actions	Immune activation B- and T-cell proliferation ↑ Natural killer cell activity Macrophage cytokine production	T helper cell, B-cell activation Increased natural killer cell activity Cytokine production	B cell differentiation Antibody synthesis Acute phase protein induction Hematopoiesis	IL-1 release Macrophage activation T-cell activation Fever Antitumor activity	Wound healing Extracellular matrix synthesis Immunosuppression	Macrophage activation MHC expression Fever Acute-phase protein induction Antitumor activity
CNS production Effects of cytokine on glia	Astroglia/microglia Microglial proliferation Induce microglia IL-6 expression Autocrine IL-1 induction	Astroglia/microglia Oligodendrocyte maturation	Astroglia/microglia Astrogliosis ↓ VCAM-1 Induce IL-6, NGF production IL-6 expression ↓ ICAM-1 expression	Astroglia/microglia ICAM-1, VCAM-1 production Nitric oxide production Astrogliosis MHC class 1 and II expression NGF production	Astroglia/microglia TGF-beta expression ↓ TNF-alpha, complement, chemokines ↓ ICAM-1, VCAM-1 expression Induce IL-6 production ↓ Proliferation ↓ Class II MHC, CD40 expression ↓ IL-1, IL-6, IL-12 production	Astroglia/microglia IFN-gamma expression Astrogliosis Induce ICAM-1, VCAM-1 expression Induce TNF-alpha, IL-12, IL-10 production Induce nitric oxide production Induce class II MHC, CD40 expression
Neuronal effects	Direct neurotoxicity Apoptosis	Promotes survival	↑ IL-6 expression Survival factor Neurotoxic factor	ICAM-1, VCAM-1 production Nitric oxide production	TGF expression Survival factor esp. dopaminergic neurons Neuroprotective activity	IFN expression Class 1 MHC expression
Other CNS actions	HPA axis stimulation Fever Sleep	BBB disturbance HPA axis stimulation ? analgesic activity	BBB disturbance Intrathecal IgG production Fever	Demyelination Fever Sleep	Apoptosis ↓ Prolactin secretion CRF	Fatigue Feeding behavior Temperature regulation Widespread
CNS localization	Brain stem Hippocampus Hypothalamus	Hippocampus Locus coeruleus Forebrain	Hippocampus Prefrontal cortex	Widespread	Widespread	
Neurotransmitter effects	↑ Noradrenergic, dopaminergic, serotonergic GABAergic activity	↑ Noradrenergic, dopaminergic, cholinergic activity	↑ Noradrenergic, dopaminergic, serotonergic activity	↑ Catecholamines	?	↓ Serotonergic/noradrenergic activity
Cognitive effects	Sickness behavior Sleep regulation Stress modulation	Memory delirium	Stress modulation	Cognitive processing	?	Cognitive processing Psychosis Suicidal ideation
Disease associations	AD, stroke, MS, ADC	MS, ADC	AD, stroke, MS, ADC	AD, stroke, MS, ADC	AD, stroke, PD, MS, ADC	MS

AD = Alzheimer's disease; ADC = acquired immunodeficiency disease syndrome; CD40 = B-cell-associated molecule CD40; BBB = blood brain barrier; CNS = central nervous system; GABA = gamma-aminobutyric acid; HPA = hypothalamic-pituitary-adrenal axis; Ig = immunoglobulin; ICAM = intercellular adhesion molecule; IFN = interferon; IL = interleukin; MHC = major histocompatibility complex; MS = multiple sclerosis; NGF = nerve growth factor; PD = Parkinson's disease; VCAM = vascular cellular adhesion molecule.

such as complement proteins C1s and C1r,<sup>58</sup> resulting in an upregulation of the inflammatory process.

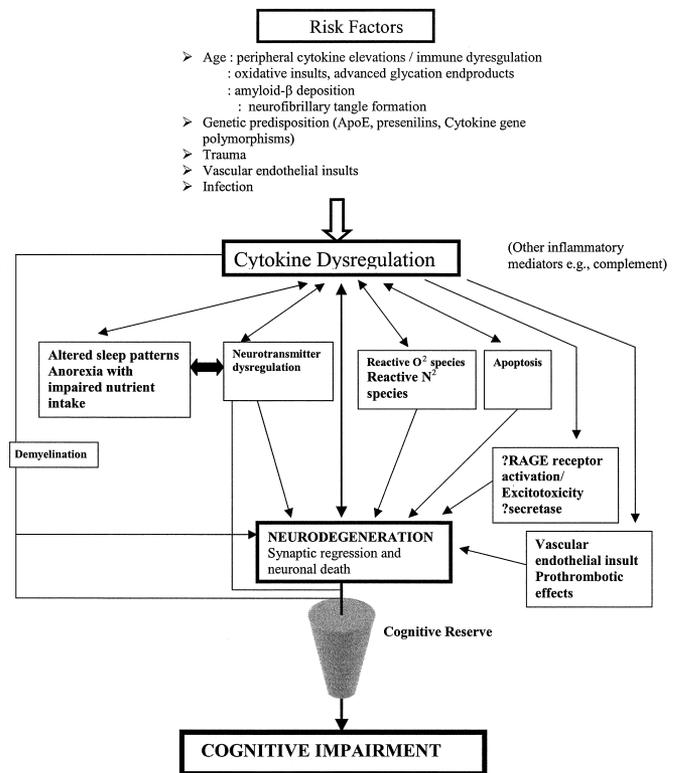
Cytokines can activate glial cells *in vivo*<sup>59,60</sup> and, conversely, glial cells can produce cytokines when activated.<sup>61</sup> Specific combinations of cytokines can induce dose-dependent neuronal injury,<sup>62</sup> supporting the concept of cytokines acting as direct mediators of neuronal injury upon release by activated microglia or astrocytes. In addition, cytokines, amyloid- $\beta$ , and complement proteins can activate microglia *in vitro* to produce free radicals, glutamate, or complement factors.<sup>63</sup> There appears to be a differential regulation of cellular expression of IL-1 $\alpha$ , IL-1 $\beta$ , and IL-6 within the CNS, with various patterns of cytokine secretion seen, depending on the mode of injury leading to the inflammatory response.<sup>64</sup> The debris created by neuronal damage may serve to further activate microglia and astrocytes, leading to a vicious cycle of damage.<sup>65</sup>

It is likely that numerous mechanisms operate interactively to promote neuronal injury in the setting of cytokine exposure. These include but are not limited to the complement cascade, excitotoxic glutamate receptor-mediated damage, oxidative stress, abnormal neurotransmission, and induction of nitric oxide. Human glia can produce nitric oxide in response to IL-1 challenge, potentiated by IFN- $\gamma$  and leading to apoptotic neurodegeneration; excitotoxic synaptic transmission is also implicated.<sup>66–69</sup>

Cytokine-mediated central inflammatory processes thus involve a number of diverse mechanisms and may proceed in parallel with nondegenerative consequences of peripheral or central cytokine dysregulation to affect cognition (Figure 1). The effects of cytokines on cognition thus function in two directions, with systemic cytokines able to signal the CNS and with the effects of cytokines on behavior causing systemic effects that eventually negatively affect cognition. The cognitive manifestations of the aforementioned neurodegenerative processes will occur after insults, whether acute or chronic, breach an individual's homeostatic limit, a so-called "cognitive reserve," possibly determined by synaptic density or plasticity.

### Interleukin-1

Capable of neurotrophic and neurotoxic actions, IL-1 is thought to be central to CNS inflammatory modulation in response to CNS injury or systemic insult but has been implicated in activities as diverse as fever, sleep, and neuroimmunoendocrine modulation. Constitutive expression of IL-1 $\beta$ , IL-1 $\gamma$ , and IL-1 $\alpha$  by microglia, astrocytes, neurons, and endothelium has been documented.<sup>70,71</sup> In addition, IL-1 receptors have been detected in the rat hippocampus, hypothalamus, cerebellum, and cerebrovascular endothelium.<sup>72,73</sup> Increases in IL-1 have been documented after excitotoxic injury, LPS challenge, mechanical damage, and ischemia.<sup>74</sup> IL-1 induces microglial proliferation,<sup>75</sup> stimulates microglial expression of IL-6,<sup>65</sup> and mediates autocrine effects to activate microglia and further promote IL-1 expression. Injection of IL-1 into cerebral ventricles or specific brain regions of the rat produces an exacerbation of neuronal damage, regardless of whether the primary insult is ischemia, trauma, or excitotoxins, and appears to preferentially damage "threatened" cells.<sup>70</sup> Conversely, inhibition of IL-1 decreases brain damage *in vivo*.<sup>76</sup>



**Figure 1.** Possible mechanisms of cytokine-induced cognitive impairment.

Intraventricular and peripheral administration of IL-1 leads to CNS release and turnover of norepinephrine, serotonin,<sup>27</sup> tryptophan,<sup>77</sup> and dopamine.<sup>78</sup> IL-1 can induce neuronal acetylcholinesterase expression and increase the enzyme's activity, thus promoting a cholinergic deficit.<sup>79</sup> In addition, direct inhibition by IL-1 of acetylcholine release from hippocampal neurons has been documented.<sup>80</sup> Injection of IL-1 $\beta$  into the basal forebrain of rats led to an increase in cortical release of the neurotransmitter gamma amino butyric acid (GABA).<sup>81</sup> It has been postulated that increased GABAergic tone results in cortical and subcortical neurodegeneration, highlighting a mechanism whereby IL-1 $\beta$  may directly incite a neurodegenerative process.

IL-1 may mediate excitotoxic neurodegeneration. Activation of excitotoxic amino acid receptors enhances expression of IL-1 $\beta$ .<sup>82</sup> Conversely, IL-1 $\beta$  appears capable of modulating glutamate excitation in hippocampal neurons.<sup>83</sup> In addition, IL-1 $\beta$  and TNF- $\alpha$  have been shown to inhibit astrocyte induction of glutamine synthetase,<sup>84</sup> an enzyme that converts excess glutamate to glutamine to protect neurons from excitotoxicity.

Induction of nitric oxide synthase in perivascular glia is thought to mediate some of the CNS dysfunction associated with therapeutic administration of IL-1.<sup>31</sup> The resultant nitric oxide production may promote neurodegeneration through generation of reactive nitrogen species (e.g., peroxynitrite).<sup>81</sup> IL-1 $\beta$  also appears to be a mediator of apoptosis, as suggested by the finding that apoptotic mechanisms are blocked by IL-1 $\alpha$  infusion.<sup>85</sup> A group of proteases, for example ced3, which are thought to be involved in apoptosis, are structurally related to the IL-1 converting enzyme.<sup>86,87</sup> Finally, *in vitro* and *in vivo* studies suggest ad-

ditional neurotoxic properties of IL-1 via induction of other proinflammatory cytokines; enhanced calcium entry; free radical release; BBB damage; and activation of adhesion molecules, complement acute-phase proteins, and amyloid- $\beta$  protein.<sup>70</sup>

### Behavioral Effects of IL-1

Peripheral administration of IL-1 has elicited diverse cognitive-behavioral effects, including decreased exploratory behavior,<sup>88</sup> decreased locomotor activity,<sup>23</sup> decreased operant responding for food rewards,<sup>89</sup> inhibition of sexual behavior,<sup>90</sup> sleep promotion,<sup>91</sup> anorexia,<sup>92</sup> and anxiogenic reactions.<sup>23</sup> It is thought that hippocampal function is impaired by peripheral administration of IL-1, leading to impaired ability to learn complex environmental relations but not simple motor procedures.<sup>93</sup> Consistent with this, IL-1 $\beta$  led to impaired consolidation of spatial information during water maze performance in rats.<sup>94</sup> Finally, it has been theorized that age-associated cognitive impairment relates to an increase in hypothalamic IL-1 $\beta$ .<sup>95</sup> IL-1 $\beta$  is thought to damage the neuronal membrane via lipid peroxidation, thus leading to decreased long-term potentiation, an electrophysiological index of synaptic plasticity linked to memory and learning.

### Interleukin-2

IL-2 enhances dopaminergic transmission.<sup>96,97</sup> Anhedonia, manifested by blunted reward processes and thought to be mediated by dopaminergic mechanisms, appears to be a consequence of acute IL-2 administration.<sup>23</sup> Chronic peripheral administration has been associated with rat hippocampal neurodegeneration and suppression of hippocampal long-term potentiation,<sup>98</sup> leading to impaired memory performance,<sup>99</sup> and with suppression of afferent sensory transmission in the primary somatosensory cortex, leading to poor spatial learning.<sup>100</sup> Administration to human subjects has led to cerebral vasculitis, lengthening in evoked cognitive potential (P300) latencies, and frontal electroencephalography abnormalities.<sup>22,101</sup> Despite its adverse CNS side-effect profile, it has become apparent that IL-2 also serves as a neuroregulatory molecule in the CNS, with diverse actions, such as promotion of neuronal survival, stimulation of oligodendrocyte proliferation and maturation, hypothalamic-pituitary axis stimulation, and possibly analgesic properties.<sup>102</sup>

### Interleukin-6

The CNS functions of IL-6 are not fully established, with concentrations typically at the lower limits of detection during normal physiological states.<sup>64</sup> More commonly, IL-6 shows adverse effects, with induction of acute phase proteins, increases in vascular permeability, and lymphocytic activation. IL-6 is capable of enhancing leukocyte recruitment via chemokine and adhesion molecule upregulation.<sup>103</sup> IL-6 also causes reactive gliosis via microglial or astrocytic activation.<sup>40</sup> Long-term IL-6 treatment enhances the response to N-methyl-D-aspartate; thus, excitotoxic mechanisms may mediate the neuropathology seen with chronically elevated IL-6 levels.<sup>104</sup> IL-6 also facilitates neuroendocrine communication, stimulating the hypothalamic-pituitary-adrenal (HPA) axis and causing adrenocorticotrophic hormone (ACTH) release.<sup>105</sup>

In other situations, IL-6 is antiinflammatory, inhibiting TNF $\alpha$  synthesis and inducing expression of IL-1 receptor antagonist and the TNF- $\alpha$  soluble receptor.<sup>40</sup> Acute IL-6 administration protects against excitotoxic<sup>57</sup> and ischemic<sup>106</sup> brain damage in rats *in vivo*.

Systemic IL-6 administration leads to increases in noradrenergic and serotonergic neurotransmission.<sup>107</sup> Similar to IL-1 and IL-2, peripheral IL-6 administration in mice decreased the amnesic effects of the muscarinic antagonist scopolamine, thus suggesting that the cytokine interacts with the cholinergic system.<sup>108</sup>

IL-6-deficient mice show sensory impairments and impaired axonal regeneration.<sup>109</sup> Transgenic mice expressing high IL-6 levels show ataxia, tremor, motor impairment, and seizures, with upregulation of acute phase response genes and other inflammatory response genes, including those for intercellular adhesion molecule-1, TNF- $\alpha$ , and IL-1.<sup>4</sup> There is a major impairment in synaptic plasticity in IL-6 transgenic mice, manifested cognitively by defects in avoidance learning.<sup>110</sup>

### The Interferons

IFN- $\alpha$  is thought to possess neuroregulatory functions including behavior, temperature regulation, and control of feeding patterns.<sup>111</sup> Administration of IFN- $\alpha$  to humans results in an array of CNS side effects, including nausea, fatigue, anhedonia, confusion, coma, paresthesia, psychomotor slowing, apathy, thought blockade, sexual dysfunction, visual disorientation anxiety, and depression. Recipients of IFN- $\alpha$  therapy typically report reduced alertness, with sustained slowing of reaction times at higher doses.<sup>112</sup> After several weeks of treatment, a syndrome of subjective memory loss, depression, and impaired motor and executive functioning, consistent with frontal-subcortical impairment, has been identified.<sup>113</sup> The mechanisms of IFN- $\alpha$ -induced neurotoxicity may include cytokine, neurotransmitter, or neuroendocrine effects or a combination thereof. Some of these CNS effects may occur via induction of IL-1, IFN $\gamma$ , and TNF $\alpha$ , all of which are known to produce potent CNS effects. IFN $\alpha$  acts acutely as a central dopamine agonist,<sup>114</sup> whereas long-term administration leads to dopamine receptor downregulation and serotonin depletion, which would more consistently explain its cognitive effects.<sup>113</sup>

### ALZHEIMER'S DISEASE

A state of chronic brain inflammation characterizes AD, the most common neurodegenerative disease associated with progressive cognitive decline. Cytokines influence a number of different mechanisms that may induce or accelerate the development of neurodegeneration and the AD phenotype.<sup>115,116</sup> The recent Neuroinflammation Working Group workshop on inflammatory mechanisms in AD<sup>116</sup> considered various hypotheses about the activation of microglia and astrocytes by cytokines and Ab protein as critical to AD development. It remains uncertain "whether inflammatory mechanisms (are) actually causing damage in AD or . . . present merely to remove the detritus from other, more primary pathologic processes."<sup>116</sup> However, cytokine-mediated inflammation is likely to exacerbate disease progression in association with factors such as glutamate excitotoxicity and reactive oxygen intermediate toxicity. Consistent with this reasoning, subjects with late-

stage dementia have been shown to have higher levels of IL-6 and TGF- $\beta$  mRNA expression in the entorhinal cortex and superior temporal gyrus at autopsy.<sup>117</sup>

It is widely assumed that increased levels of the Ab protein are a likely precipitant of AD, but one of the stronger arguments against the centrality of amyloid to the pathogenesis of AD is that the amount of solid amyloid deposition (fibrillar Ab aggregates) does not correlate with the degree of cognitive impairment or the progression of the clinical disease.<sup>118</sup> Thus, some cognitively intact older people have shown large amounts of amyloid deposition at autopsy, but, recently, a correlation has been established between novel amyloid species (e.g., small Ab oligomers) and disease severity.<sup>119</sup> Inflammatory mediators derived from reactive astrocytes, activated microglia, and leukocytes are differentially seen in early-stage diffuse amyloid plaques rather than in “burned-out” plaques,<sup>120</sup> suggesting that inflammatory plaques should show a stronger correlation with cognition.

### PERIPHERAL CYTOKINES AND ALZHEIMER'S DISEASE

The literature has been somewhat inconsistent in regard to peripheral cytokine dysregulation in AD. Increased levels of IL-1 $\beta$ , IL-6, or TNF- $\alpha$  have been found in peripheral blood<sup>11,121–125</sup> or autopsy specimens<sup>126,127</sup> of patients with mild to moderate late-onset AD. After LPS stimulation, patients with AD also produced higher levels of IL-1 $\beta$ , IL-6, IL-10, and TNF- $\alpha$  than normal controls.<sup>128</sup> However, other studies did not detect such blood cytokine elevations.<sup>128–130</sup> Reports conflict regarding cerebrospinal fluid (CSF) IL-6 and IL-1 levels in patients with AD.<sup>131–133</sup> Increased levels of the acute phase reactant  $\alpha$ -1-antichymotrypsin and of neopterin, a circulating marker of cytokine-induced reticuloendothelial cell system activation, have been found in small AD samples,<sup>134,135</sup> although these changes have not been found invariably.

A unique longitudinal study of paired CSF and serum samples from eight patients pathologically confirmed with AD found no correlation between inflammatory mediators and change in cognitive status or progression of temporal lobe atrophy on computed tomography scans,<sup>136</sup> but tissue TNF- $\alpha$  levels were lower in the frontal cortex, superior temporal gyrus and entorhinal cortex in the AD cohort.

Peripheral cytokine elevations evidenced in AD may simply represent a “spillover” from central inflammatory processes.<sup>134</sup> In support of this hypothesis, intracerebroventricular administration of IL-1 $\beta$  results in peripheral IL-6 elevations in rats<sup>137</sup> and primates.<sup>138</sup> Nevertheless, in considering the fact that cytokines function as mediators for bidirectional communication between central and peripheral neuroendocrine and immune systems, it is possible, that both sides of the argument hold some relevance.

The role of inflammation in early stages of AD is very likely, in view of the presence of complement C1q immunoreactivity in the amyloid deposits<sup>139</sup> of those in preclinical stages, the so-called mild cognitive impairment (MCI). Individuals with MCI are typically in their 70s and 80s and are able to function quite normally, often with few complaints about cognitive capacity, despite identifiable deficits on neuropsychological testing. If death occurs soon

after the recognition of these changes, major neurodegeneration is often found.<sup>140–142</sup>

Genetic research is beginning to identify susceptibility genes that may influence the inflammatory process in AD. Possession of the C allele of the gene encoding IL-6 is associated with reduced systemic IL-6 activity and has been shown to decrease the risk of sporadic AD and delay its initial onset.<sup>143</sup> Likewise, common population polymorphisms in the interleukin genes IL-1A<sup>144</sup> and IL-1B<sup>145</sup> are associated with increased risk of early onset AD. Thus, inherited variations in inflammatory response mechanisms may influence AD pathogenesis.

AD, although phenotypically manifested as cognitive deficits, exhibits pathologic traits that are suggestive of a systemic disorder. Expression of amyloid precursor protein (APP), from which Ab peptide is derived, has been demonstrated in many tissues other than brain in Alzheimer subjects and in normal mammals, including skeletal muscle and liver.<sup>146</sup> It has been demonstrated that peripherally administered Ab peptide penetrates the BBB,<sup>147</sup> raising the possibility of a certain degree of peripheral origin for CNS amyloid accumulation. A significantly higher level of Ab peptide in temporalis muscles has been demonstrated in patients with AD than in cognitively normal age-matched controls, suggesting a potential source of hematogenous Ab peptide in AD.<sup>148</sup> In addition, deposits of the Ab peptide in skin are more common in patients with AD than in non-AD controls.<sup>146,149</sup> Peripheral alterations in APP metabolism have been described not only in the brain, but also in the periphery.<sup>150,151</sup> Because “senile” amyloids accumulate in other vital organs to varying degrees,<sup>152</sup> it is imperative to analyze nonneural amyloids in individuals whose brains are characterized for the neuropathology of AD. This effort might show further relationships between peripheral and central inflammatory processes of aging.

### Nonsteroidal Antiinflammatory Drugs

Findings from epidemiological studies and some small clinical trials<sup>153–157</sup> that nonsteroidal antiinflammatory drug (NSAID) users have a lower risk of AD, with indications of dose effects, has sparked much interest in inflammatory mechanisms in AD. Particular NSAIDs are major candidates in the prevention of AD, as recent post hoc studies of community-dwelling older people in Cache county, Utah;<sup>158</sup> Rotterdam;<sup>159</sup> and the Baltimore Longitudinal Study<sup>160</sup> have shown. Inverse associations between NSAID use and AD have been reported<sup>161,162</sup> as having slower progression rates of AD.<sup>163</sup> Old-old people may be less responsive to cognitive benefits of NSAIDs.<sup>164</sup> Reduction of AD risk appears to require at least 2 years of NSAID use during cognitive health.<sup>165</sup> However, in a large prospective cohort study of 2,765 subjects, no consistent protective effect of NSAID use on cognitive functioning could be demonstrated after 3 years.<sup>166</sup> In addition, NSAID use has been associated with deterioration in immediate word recall,<sup>167</sup> delirium,<sup>168</sup> psychosis,<sup>169</sup> and cognitive impairment.<sup>170</sup>

Recently, Weggen et al.<sup>171</sup> added to potential mechanisms of NSAIDs with their evidence that certain NSAIDs, such as ibuprofen, decrease amyloid-beta-42 production independently of prostanoid synthesis. However, more than half of the NSAIDs found effective by In't Veld et al.<sup>159</sup> did

not influence amyloid-beta-42 production. Furthermore, aspirin did not affect amyloid-beta-42 at the highest concentrations tested<sup>171</sup> yet was almost as effective as other NSAIDs in the Cache County and Baltimore studies. The Cache County and other studies showed significant effects of aspirin in reducing AD risk accounted for over-the-counter use, in contrast to the Rotterdam study, which did not find an effect of aspirin and was largely weighted by prescription NSAIDs.<sup>172</sup>

Animal models support these effects of NSAIDs. Oral ibuprofen attenuated neurodegeneration in APP transgenic mice<sup>173</sup> and lowered amyloid-beta-42 levels relative to amyloid-beta-40 *in vivo*<sup>171,173</sup> and *in vitro*.<sup>171</sup> We do not know of studies on aspirin in AD transgenic mice.

One possible molecular mechanism for the proposed beneficial effects of NSAIDs is their ability to inhibit IL-1 $\beta$ -induced IL-6 release from human astrocytes *in culture*.<sup>174</sup> One of their targets, the ligand-activated nuclear receptor peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), might also mediate the potential central antiinflammatory effects of NSAIDs in AD. PPAR $\gamma$  agonists inhibit Ab-stimulated production of IL-6 and TNF- $\alpha$  by microglia.<sup>175</sup> In addition, PPAR $\gamma$ -induced inhibition of inducible nitric oxide synthase can prevent cytokine-induced apoptotic cell death.<sup>176</sup>

## CYTOKINES AND VASCULAR DEMENTIA

Although not directly explored as with AD, there is a strong theoretical basis for considering cytokines in the pathophysiology of vascular dementia. By influencing the response to ischemia, cytokines may determine the point at which the burden of serial ischemic insults overcomes an individual's cognitive reserve threshold. In addition, the atherogenic and prothrombotic effects of cytokines may directly influence pathogenic events.

Cytokines can directly influence the coagulation cascade. IL-1, IL-2, IL-6, and TNF- $\alpha$  have been shown to stimulate components of the coagulation system, with diverse mechanisms implicated, such as conversion of the endothelium from an antithrombotic to a prothrombotic surface, stimulation of tissue factor production with resultant activation of intrinsic and extrinsic coagulation pathways, inhibition of the fibrinolytic system, and induction of platelet-activating factors.<sup>177,178</sup> There is a positive correlation between the circadian rhythms of IL-6 and plasma fibrinogen,<sup>179</sup> and it appears that IL-6-stimulated hepatic fibrinogen production may play a role in the tendency toward morning arterial ischemic events. Cytokines such as IL-1 and TNF- $\alpha$  are known to modulate endothelial functions that govern the formation and stability of blood thrombi,<sup>180</sup> and IL-2 may induce disseminated intravascular coagulation.<sup>178</sup> The modulation of prothrombotic risk by peripheral proinflammatory cytokines is seen in inflammatory bowel disease, where complications as diverse as peripheral venous thrombosis, stroke, leukoariorosis, and polyneuropathy suggest both macrovascular insult and microangiopathy.<sup>181</sup>

In addition to their prothrombotic effects, cytokines can influence many steps of the atherogenic process. IL-1 $\beta$ , IFN- $\gamma$ , and TNF- $\alpha$  can induce smooth-muscle degeneration by apoptosis, whereas TNF $\alpha$ , IL-1 $\beta$ , or IL-6 may promote cellular adherence to endothelial cells.<sup>74</sup> IL-1 and TNF- $\alpha$ , for example, have been shown to regulate produc-

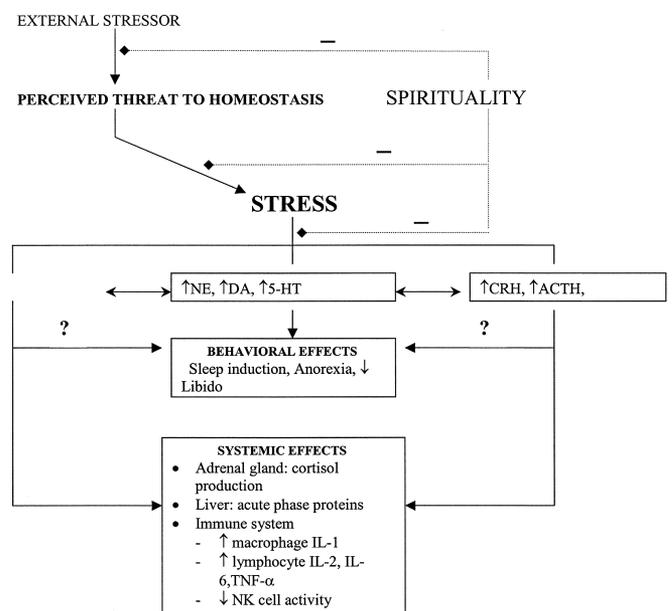
tion of vascular cell adhesion molecules and monocyte chemoattractant protein-1, both of which influence cell migration to the lesions and mediate increased interactions between monocyte/macrophage cells and cerebrovascular endothelial cells.<sup>180</sup> TNF- $\alpha$ , IL-6, and IL-10 have also been shown to cause local arterial vasoconstriction via direct effects on endothelial cytokine receptors<sup>182</sup> or indirectly via modulation of inducible nitric oxide synthase.

## STRESS, DEPRESSION, AND COGNITIVE INFLUENCES ON SYSTEMIC IMMUNE FUNCTIONING

### Stress and the HPA Axis

In the preceding text, we have shown that immunological cytokines signal the brain. The brain, in turn, regulates the immune system via generation of neurotransmitter signals, which travel to noradrenergic and cholinergic terminals, innervating immunologically active tissues such as the thymus and bone marrow.<sup>183</sup> In addition, lymphocytes and monocytes have been shown to possess neurotransmitter and hormone receptors.<sup>184</sup> It is also evident that cognitive responses to external stimuli are capable of influencing cytokine production, and immunologic equilibrium. Stress, the body's reaction to perceived physical or psychological disruptions to its homeostasis, is a prime example whereby cognitive perceptions of stimuli may influence immune functioning (Figure 2).

Stress causes activation of central noradrenergic, dopaminergic, and serotonergic pathways, the HPA axis, and the sympathetic nervous system. Coupled with such responses, stress and depression are often associated with impaired immune function.<sup>3,185-187</sup> A growing body of



**Figure 2.** Central cognitive processing and systemic cytokine responses (the example of stress). ACTH = adrenocorticotropic hormone; CNS = central nervous system; CRH = corticotropin-releasing hormone; DA = dopamine; HT = hydroxytryptamine; IL = interleukin; NE = norepinephrine; NK = natural killer; TNF- $\alpha$  = tumor necrosis factor-alpha.

literature<sup>188</sup> demonstrates the diverse effects of stressors on cytokine production. It has been reported that physical or psychological stress increases IL-6 concentrations.<sup>189–191</sup> In animal models, acute restraint stress or tail shock induces hypothalamic IL-1 $\beta$  and IL-1 $\beta$  mRNA expression.<sup>192,193</sup> Conversely, administration of cytokines produces alterations in monoamine neurotransmitter systems that resemble those seen in states of stress.<sup>25,45,107</sup> It would appear that cytokines may be at the interface between the cognitive perception of a stressor and its physiological sequelae.

Brain IL-1 $\beta$  may be involved in mediating some of the consequences of stress exposure via its activating effects on the HPA axis.<sup>194,195</sup> Centrally administered IL-1 $\beta$  produces similar consequences to those produced by stressors, including increased plasma ACTH and glucocorticoid levels<sup>196</sup> and increased monoaminergic neuronal activity. IL-1 $\beta$  induces hypothalamic release of corticotropin-releasing hormone (CRH), a central regulatory neuropeptide that appears to coordinate the neuroendocrine response to stress via activation of the HPA and sympathetic nervous system.<sup>194,197–199</sup> IL-6, IL-2, and IFN $\alpha$  also activate the HPA axis in humans, although IFN- $\alpha$  shows variable effects.<sup>105,200–202</sup> Typically, the glucocorticoid response to stress leads to immunosuppression, with corticosterone inhibiting the effects of IL-1 $\beta$ .<sup>203</sup> In keeping with this concept of tonic inhibition of the immune response during stress, adrenalectomized animals manifest a stress response that is associated with increased IL-1 $\beta$  in the hypothalamus, hippocampus, cerebellum, and nucleus tractus solitarius.<sup>204</sup> Glucocorticoids can also act synergistically with cytokines; for example, glucocorticoids potentiate IL-1 and IL-6 expression of acute phase proteins.<sup>205</sup> In addition, glucocorticoids upregulate the expression of certain cytokine receptors (IL-1, IL-2, IL-4, IL-6, IFN- $\gamma$ , TNF- $\alpha$ ).<sup>206</sup>

Chronic stress is often maladaptive. Older spousal caregivers of demented patients show high rates of depression,<sup>207</sup> impaired immune function with alterations in natural killer cell response to cytokines,<sup>208</sup> impaired wound healing,<sup>209</sup> and a higher frequency of upper respiratory tract infections.<sup>210</sup> Significant IL-6 elevations have been reported in AD caregivers,<sup>211</sup> suggesting that significant chronic stress can cause cytokine dysregulation. Cognitive processing of stressors and the resultant effects on cytokines, centrally and peripherally, can therefore have effects on a variety of tissues as attempts to maintain physiological homeostasis in the face of persisting stimuli result in dysregulation of immune and endocrine axes.

### Depression

The concept of “pseudodementia” takes on a new level of meaning as we begin to understand the overlapping roles of serum cytokines in depression and cognitive disorders. The overlap between symptoms of “sickness behavior” induced by peripheral cytokine administration and of major depression supports the consideration of cytokines as part of a biological mechanism of depression. The monoamine hypothesis<sup>212</sup> proposes that a deficit of brain norepinephrine or serotonin may be causally involved in the symptoms of major depressive illness. In support of this theory, IL-1 $\beta$  modulates central serotonergic function, and serotonergic neurons possess IL-1 $\beta$  receptors.<sup>213</sup> IL-1 $\beta$  may deplete serotonin from the synaptic cleft by directly acti-

vating serotonin transporter mechanisms,<sup>214</sup> leading to decreased serotonergic function. The monoamine hypothesis fails to account for the dysregulation in HPA axis functioning,<sup>215</sup> but Smith<sup>216</sup> proposed a “macrophage theory of depression” in which excessive secretion of monokines; changes in CRF, ACTH, prolactin, and cortisol; and dysregulation of the HPA axis play a pathogenic role.

Immune activation, with increases in serum IL-6, soluble IL-2 receptor, IL-1, IL-1ra, and IFN- $\gamma$  have been reported in depressed patients.<sup>217–221</sup> In addition, treatment-resistant depression appears to be associated with higher cytokine elevations.<sup>221</sup> Conversely, peripheral administration of cytokines such as IL-2 or IFN often leads to depressive symptoms and stimulation of the HPA axis. Antidepressant therapy has been shown to decrease blood levels of IL-6 in humans,<sup>222</sup> although such findings have not been consistently reported.<sup>220</sup> The HPA axis activation and hypercortisolemia often seen in depressed patients may represent increased CRF secretion induced by cytokines IL-1 and IL-6. Usually, glucocorticoids effect a negative feedback on immune cells to inhibit production of inflammatory cytokines,<sup>223</sup> but there appears to be a defect in the negative feedback of cortisol on CRF and cytokine secretion in depressed patients.<sup>224</sup>

It is conceivable that an age-related peripheral cytokine dysregulation could promote a small-scale sickness behavior response, with the possibility that cognitive manifestations could therefore resemble the pseudodementia phenotype. Certain cytokines could produce similar cognitive manifestations through their atherogenic and prothrombotic effects, leading to cerebrovascular insult and vascular depression.

### Spirituality and Cognitive Influences on Systemic Immune Functioning

In keeping with our model of an intimate relationship between the CNS and the immune system, religion serves as an example of how a pervasive cognitive system influencing interactions with one's environment may modulate the effects of stress on the immune system. There is a further, as yet unaccounted for, contribution of religious participation to the health<sup>225</sup> and longevity<sup>226</sup> benefits of healthy lifestyle approaches and increased social support. In an attempt to explain the link between religiosity and well-being, investigators have explored the influence of religiosity on serum cytokines.

Koenig et al.<sup>227</sup> showed an inverse correlation between religious attendance and IL-6 levels, controlling for socio-demographics, chronic illness, and physical functioning. Religiosity is often associated with broader and more-integrated social support networks and reduced stress.<sup>228</sup> It may be that such behaviors suppress stress responsive brain areas, alter cognitive perception of stressors, and buffer the effect of stress on the immune system.

### Other Mechanisms of Cytokine-Mediated Cognitive Impairment

In addition to the aforementioned direct mechanisms whereby cytokines may affect cognition, a number of indirect pathways for a peripheral cytokine influence on cognition exist. These indirect mechanisms include but are probably not limited to cytokine-induced anorexia with

resultant micronutrient deficiency, impaired sleep regulation, and endocrine interactions. Rather than a comprehensive analysis of each field, the following section is intended to serve as an indication that the diversity of cytokine actions suggests the potential for concurrent mechanisms of cognitive insult.

### Nutrition

The idea that cytokine-driven anorexia could contribute to cognitive impairment has some support from the literature. IL-1, IL-6, TNF- $\alpha$ , and leukemia inhibitory factor have been linked to cachexia in cancer and in animal models of sickness behavior.<sup>229</sup> Both intracerebroventricular and peripheral TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, and IFN administration suppress food intake,<sup>230</sup> but it is unclear whether this relates solely to effects on neurotransmission (e.g., serotonergic inhibitory effects in the lateral hypothalamus)<sup>231</sup> or whether other mechanisms (e.g., CRH or suppression of glucose-sensitive neurons)<sup>92</sup> are involved. Peripherally mediated mechanisms have also been cited, such as inhibition of gastric emptying and intestinal motility.<sup>229</sup> Leptin is a molecule thought to provide a mechanism for communication between adipose tissue and the CNS. Homologies exist between the leptin receptor and cytokine receptors,<sup>232</sup> which provides some mechanistic overlap in the physiology underlying cytokine-mediated anorexia.

It is conceivable that chronic cytokine elevations could induce a state of anorexia that eventually leads to micronutrient deficiencies. Deficiencies of B vitamins involved in one-carbon metabolism have been associated with cognitive impairment,<sup>233,234</sup> perhaps due to lower production of S-adenosylmethionine and methionine and resultant impairment of myelin, acetylcholine, or membrane phospholipid metabolism. Goodwin et al.<sup>235</sup> have associated low folate, vitamin B<sub>12</sub>, vitamin C, and riboflavin blood levels with poor memory and nonverbal abstract thought performance testing. Because homocysteine has emerged as an independent risk factor for vascular disease,<sup>236</sup> it is conceivable that B-vitamin deficiencies with resultant hyperhomocysteinemia could also contribute to cognitive impairment via microvascular or macrovascular insult.

Caloric restriction has emerged as one of the more promising strategies for prolongation of the life span in a number of species. In support of a beneficial effect of caloric restriction on brain function are reports that caloric restriction reduced the age-associated induction of inflammatory and oxidative stress genes<sup>237</sup> and increased levels of brain-derived neurotrophic factor<sup>238</sup> in the mouse brain. Despite this, reports of beneficial effects of caloric restriction on cognitive functioning have not been forthcoming.

### Sleep Regulation

A neural cytokine network appears to be involved in the regulation of physiological sleep. Peripheral inflammatory stimuli may produce a rise in central IL-1 and TNF, with resultant somnogenic effects, as seen in the sickness behavior response. In addition to the direct hypnagogic effects of cytokines, sleep promotion is presumed to result from an interplay between cytokines and components of the neuroendocrine system, including growth hormone releasing hormone, growth hormone, somatostatin, melatonin, and insulin.<sup>91</sup> Diurnal rhythms of TNF- $\alpha$  mRNA and IL-1 $\beta$

mRNA correspond with sleep-wake cycles, and synergistic interactions between these two cytokines may promote sleep induction.<sup>91,239</sup> Peripheral administration of IL-6 in humans has been shown to cause fatigue and reductions in rapid-eye-movement (REM) sleep.<sup>240</sup> Conversely, sleep deprivation has been found to cause daytime IL-6 elevations.<sup>241</sup>

Intracerebroventricular administration of IL-1 $\alpha$ , IL-1 $\beta$ , or TNF- $\alpha$  leads to an increase in non-REM sleep, whereas IL-13, TGF- $\beta$ , IL-4, IL-10, and IFN- $\alpha$  attenuate sleep.<sup>242-245</sup> In addition, granulocyte-macrophage colony-stimulating factor can promote REM sleep when infused intracerebroventricularly in rats, an effect that is thought to be mediated by activation of the nitric oxide system in the hypothalamus and subsequent release of somatostatin.<sup>246</sup>

Cognitive deficits resulting from sleep deprivation include impaired judgment and decision-making, decreased attention, and amplitude reduction in visual event-related potentials.<sup>247-249</sup> It is likely that these cognitive effects of sleep deprivation are manifested with less of an inciting stimulus in the presence of lowered cognitive reserve with advancing age, as evidenced by the frequency of delirium in hospitalized older people.<sup>250</sup> However, less clear is whether an age-related cytokine dysregulation might contribute to changes in sleep patterns with advancing age.

### FUTURE TREATMENT OPTIONS?

A number of therapeutic agents that antagonize cytokine actions have been associated with an attenuation of cytokine-mediated neuronal injury or a reduction of adverse cognitive side effects of cytokines. Etanercept, a TNF-receptor antagonist, has shown promise in the treatment of rheumatoid arthritis. Recipients of anticytokine therapies such as etanercept often claim an improved sense of well-being.<sup>251</sup> Reduction in inflammation by TNF, in theory, might preserve cognition in neurodegenerative disorders such as AD.<sup>252</sup> Although more in-depth cognitive assessment is required in future studies of such subjects, if confirmed, this will provide further evidence of a direct effect of peripheral cytokines on cognitive functioning.

Other potential anticytokine strategies include cytokine synthesis inhibitors, soluble cytokine receptors, antibodies against cytokine receptors, and other novel cytokine receptor antagonists.<sup>63</sup> Systemic postinjury administration of IL-1ra attenuates regional cell death and cognitive dysfunction after experimental brain injury in rats.<sup>253</sup> However, IL-1 knockout mice manifest detrimental effects such as impaired host response to mycobacterial infection<sup>254</sup> and impaired production of the regenerative mediator and ciliary neurotrophic factor after CNS trauma;<sup>255</sup> thus additional studies in animal models are required before further consideration of IL-1ra as a therapeutic agent.

Considerable interest surrounds the potential neuroprotective properties of estrogen against excitotoxic, oxidative, or Ab peptide-induced insult.<sup>256</sup> Estrogen administration has been shown to improve verbal memory on cognitive testing<sup>257</sup> and limit the degree of ischemic injury from stroke in humans.<sup>258</sup> Many of these proposed beneficial effects are thought to involve cytokines. Various estrogens have been found to inhibit production of IL-1 from human peripheral monocytes,<sup>259</sup> suppress expression of IL-1 and IL-6 in vascular smooth muscle cells,<sup>260</sup> suppress TNF- $\alpha$

and IFN- $\gamma$  gene expression, and activate antiinflammatory microglial pathways.<sup>261</sup> In AD models, 17- $\beta$  estradiol has been shown to decrease the Ab peptide- and LPS-induced activation of NF- $\kappa$ B and to attenuate the IL-1 $\beta$  response to Ab peptide.<sup>262</sup> In addition, estrogen has been shown to enhance clearance of Ab peptide by microglia.<sup>263</sup>

Plasma DHEA shows a progressive age-related decline in men and women. DHEA and androstenedione have been shown to inhibit IL-6 secretion from human mononuclear cells in vitro,<sup>264</sup> providing a tantalizing connection between endocrine senescence and immunosenescence. DHEA has been shown to suppress peripheral IL-4, IFN- $\gamma$ , and astrocytic TNF- $\alpha$  and IL-6 production<sup>265</sup> and thus may possess central antiinflammatory properties.<sup>266</sup> Despite its interesting inverse association with IL-6 levels and purported beneficial effects on senescence and cognition, a recent Cochrane Systematic Review<sup>267</sup> found only limited evidence of an improved sense of well-being with DHEA and no evidence that short-term DHEA administration produced cognitive improvement.

TNF- $\alpha$  and IL-1 $\beta$  production have been shown to be inhibited after dietary supplementation with fish oils containing 20- and 22-carbon n-3 fatty acids.<sup>268,269</sup> Whether dietary modulation can influence age-associated cytokine dysregulation is unclear. Caloric restriction models have suppressed age-associated increases in GFAP, a marker of reactive astrogliosis,<sup>270</sup> and in corpus callosal TGF- $\beta$ 1.<sup>271</sup> Thus, at least in aging rats, caloric restriction holds some promise as a means of delaying neurodegeneration.

An emerging literature documents the positive effects of exercise on psychological well-being, reversal of the frail phenotype, and improvements in cognitive performance. Improvements in cognitive function with exercise have been confirmed in humans<sup>272</sup> and with concordant decreases in oxidative neuronal damage in rat models.<sup>273</sup>

Long-term exercise programs, as opposed to acute exercise training, have been associated with reductions in peripheral cytokine levels. For example, a 6-month exercise program in patients with multiple cardiac risk factors led to reductions in peripheral mononuclear cell production of IFN- $\gamma$ , IL-1 $\alpha$ , and TNF- $\alpha$ .<sup>274</sup> Given that cytokines are involved in the immune activation seen in depression, exercise has been shown to be an effective treatment for depression<sup>275</sup> and is associated with improvement of certain cognitive parameters, and exercise training shifts cytokine production to a more antiinflammatory profile, it is tempting to consider that exercise-induced adjustments in peripheral cytokines are responsible for the beneficial psychological and cognitive effects of exercise.

## SUMMARY

Just as the nervous system is able to modulate immune activity, conversely, components of the immune system affect brain function. Cytokines are increasingly being recognized as mediators of such bidirectional communication. The exact schema of cytokine function within the CNS has yet to be determined and will likely involve a complex interplay between cytokines, their soluble and cell membrane receptors, and local factors related to neuronal activation and metabolism. What is relatively clear is that cytokine dysregulation occurs with age and that these cytokines are able to directly or indirectly exert influence beyond the

BBB. Because cytokines are central to a variety of neurotransmitter and neuroendocrine responses subserving cognition and to an array of neurodegenerative processes, it is conceivable that peripheral cytokine dysregulation with advancing age may directly or indirectly contribute to cognitive decline.

Despite evidence of peripheral elevations of cytokines such as IL-6 and TNF- $\alpha$  with advancing age, there is no information on the extent of cross-correlation between central and peripheral cytokine changes with aging. Nevertheless, although the association between age-related peripheral cytokine dysregulation and functional decline or mortality has been established, the correlations with lower cognitive functioning have only recently been explored from an epidemiological perspective. If emerging population studies correlate peripheral cytokine levels with the development of cognitive impairment, the "central" theories on inflammatory mechanisms in dementia may have to be modified to accommodate the role of peripheral cytokines in this process. Likewise, researchers seeking to explain the role of peripheral cytokines in cognitive disorders will have to consider the multiple effects serum cytokines may have on cognitive processing by way of their effects on the pituitary-hypothalamic axis and various behavior systems in addition to neurodegeneration. In looking beyond the traditional paradigms of cytokine-induced neurodegeneration and subsequent cognitive impairment, mechanisms that affect cognition in its broad sense will need to be explored.

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