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Physiological and Pathological Roles of Interleukin-6 in the Central Nervous System

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Abstract

The cytokine interleukin-6 (IL-6) is an important mediator of inflammatory and immune responses in the periphery. IL-6 is produced in the periphery and acts systemically to induce growth and differentiation of cells in the immune and hematopoietic systems and to induce and coordinate the different elements of the acute-phase response. In addition to these peripheral actions, recent studies indicate that IL-6 is also produced within the central nervous system (CNS) and may play an important role in a variety of CNS functions such as cell-to-cell signaling, coordination of neuroimmune responses, protection of neurons from insult, as well as neuronal differentiation, growth, and survival. IL-6 may also contribute to the etiology of neuropathological disorders. Elevated levels of IL-6 in the CNS are found in several neurological disorders including AIDS dementia complex, Alzheimer's disease, multiple sclerosis, systemic lupus erythematosus, CNS trauma, and viral and bacterial meningitis. Moreover, several studies have shown that chronic overexpression of IL-6 in transgenic mice can lead to significant neuroanatomical and neurophysiological changes in the CNS similar to that commonly observed in various neurological diseases. Thus, it appears that IL-6 may play a role in both physiological and pathophysiological processes in the CNS.

Index Entries: Interleukin-6; cytokine; neuron; central nervous system; neuropathology; neuroimmune; CNS disease; CNS inflammation.

Introduction

The cytokine interleukin-6 (IL-6) was identified in 1985 as a product from blood monocytes and was initially known as B-cell stimulatory factor-2 (BSF-2) (Hirano et al., 1985). Molecular cloning revealed that BSF-2 was identical to hepatocyte-stimulating factor, hybridoma/plasticytoma growth factor, and β-interferon, and eventually led to its renaming as IL-6 (Yasukawa et al., 1987; Van Snick, 1990). IL-6 is a soluble glycoprotein with a molecular weight of approx 26 kDa, depending on the source and preparation. Its diverse biological actions in the immune and hematopoietic systems are well known. For example, IL-6 is a mediator of signal transmis-

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sion between cells of the immune system, induces the synthesis of acute-phase inflammatory proteins in the liver, and plays an important role in the differentiation and growth of cells of the immune and hematopoietic systems (Kishimoto et al., 1992; Ershiler et al., 1994).

Recently, IL-6 has been implicated as an important regulator of cellular function in the CNS, either as a mediator of chemical signals between cells of the immune system and cells of the CNS, or as a mediator of chemical signals between cells of the CNS. However, many important details of the CNS actions of IL-6 remain to be elucidated. Issues under investigation include the CNS sources of IL-6, the cellular targets of IL-6 action, and the cellular and molecular mechanisms mediating the effects of IL-6 on CNS cells. In addition, there is considerable interest in the potential pathophysiological effects of IL-6 in the CNS, as elevated levels of IL-6 in the CNS occur in several CNS disorders. This review will summarize results from recent studies that address these issues, with an emphasis on studies in animal or cellular models. Additional information can be found in several recent reviews (Kishimoto et al., 1992, 1994, 1995; Stal and Yancopoulos, 1993; Schobitz et al., 1994; Woodroofe, 1995; Akira and Kishimoto, 1992; Akira et al., 1990; Sehgal, 1990; Jonakait, 1997; Hopkins and Rothwell, 1995; Benveniste, 1992; Hibi et al., 1990; Miyajima et al., 1992; and others noted in subsequent sections of this review).

CNS Cells that Express IL-6 and IL-6 Receptors

The expression of IL-6 and its corresponding receptor (IL-6R) in the CNS has not been investigated extensively. To date, the majority of studies have utilized methods that detect messenger RNA (mRNA) levels. Relatively little information is available on CNS levels of IL-6 or IL-6R protein, which may not correlate directly with levels of mRNA. However, localization of mRNA is an important step in the identification of cell types that are capable of producing IL-6 or IL-6R.

Several studies (mostly in animal models) utilizing the reverse transcription-polymerase chain reaction (RT-PCR) and *in situ* hybridization techniques have localized mRNA for both IL-6 and IL-6R to the parenchyma and fiber tracts of the CNS, consistent with the presence of IL-6 signaling pathways in the CNS. IL-6 and IL-6R mRNA was evident in several brain regions, including the hippocampus, striatum, hypothalamus, neocortex, cerebellum, and brain stem (Gadient and Otten, 1994a, 1995). mRNA levels tend to be higher in forebrain structures than in more caudal regions.

IL-6 and IL-6R mRNA expression appears to be developmentally regulated, with higher levels in the adult CNS compared to the immature CNS (Gadient and Otten, 1994a). However, regional differences in this general pattern have been observed. For example, in the hippocampus, IL-6 mRNA expression is highest in adulthood; whereas in the cortex, IL-6 mRNA expression is highest prenatally (Pousset, 1994). In the hypothalamus, IL-6 mRNA levels decrease during development, whereas IL-6R mRNA levels increase, suggesting that IL-6 and IL-6R expression are regulated differentially in this CNS region (Gadient and Otten, 1993). The developmental timing of the expression of the IL-6R in the hypothalamus appears to be linked to the maturation of the hypothalamic-pituitary-adrenal axis (HPA) (Gadient and Otten, 1993), consistent with a role of IL-6 in the regulation of hormone release.

At the cellular level, IL-6 and IL-6R mRNA are colocalized in several neuronal types throughout the CNS, including pyramidal and granular neurons of the hippocampus, neurons of the habenular nucleus, dorsomedial (e.g., periventricular nucleus), ventromedial, and medial preoptic nuclei of the hypothalamus, cerebellar granular neurons, and pyramidal neurons of the cerebral cortex, particularly the piriform cortex (Schobitz et al., 1992, 1993). IL-6 mRNA was also found at high levels in cerebellar Purkinje neurons, but mRNA for the IL-6R was not detected (Gadient and Otten, 1994b), possibly because the levels were too low for detection. Recently we have shown intense immunostaining for the

IL-6R in Purkinje neurons of the adult mouse (Nelson et al., 1997).

IL-6 mRNA and IL-6R mRNA are also colocalized at low levels within the white matter of fiber tracts in the forebrain, such as the corpus callosum, anterior commissure, fimbria, lateral olfactory tract, optic tract, internal capsule, and corticospinal tracts within the caudate nucleus (Yan et al., 1992; Schobitz et al., 1992, 1993). These data are suggestive of expression of both IL-6 and IL-6R by oligodendrocytes, the CNS-cell type responsible for myelination of axons of CNS neurons that comprise the fiber tracts (Yan et al., 1992). CNS astrocytes have also been reported to express mRNA for IL-6 and IL-6R, immunoreactivity for IL-6, and to produce IL-6 in vitro. Thus, a number of different cell types within the CNS have the ability to express or respond to IL-6 or to do both (Fig. 1). These results support a role for cell-to-cell signaling and perhaps autocrine regulation involving IL-6 in the CNS. However, the functional role of such pathways remains to be determined.

IL-6 Receptors and the Transduction Mechanism

IL-6 produces its biological effects on CNS cells through a specific binding protein, the IL-6R, in conjunction with a transmembrane transduction peptide referred to as gp130. The molecular structure of the IL-6R was deduced initially from the sequence of the human cloned cDNA encoding the receptor (Yamasaki et al., 1988). Like other genes encoding cytokine receptors, the gene for the IL-6R was isolated by expression cloning. Other approaches were hampered by low cellular abundance of receptors. Based on structural similarity, the IL-6R belongs to a relatively new family of receptors referred to as the cytokine receptor family. This family includes receptors for IL-2, IL-3, IL-4, IL-5, IL-7, IL-9, erythropoietin, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), and others (Taga and Kishimoto, 1992; Bazan, 1990). The IL-6R system is structurally similar to the growth-factor-receptor system and this similarity suggests that long-term changes in gene expression are one aspect of IL-6's CNS actions, although more immediate changes involving regulation of biochemical pathways may be involved as well.

Two forms of the IL-6R have been identified, a soluble form that has no membrane-spanning region and a membrane-bound form with a membrane-spanning region. The gene for the membrane-bound form of the IL-6R contains a region encoding a transmembrane protein of approx 449 amino acids with a short intracellular region of approx 82 amino acid residues (Taga et al., 1989). The N-terminus forms the extracellular domain and there is only a single transmembrane domain. The soluble form of the IL-6R is smaller than the membrane-bound form and has been proposed to result from limited proteolysis in the extracellular region of the membrane-bound receptor, a process referred to as "shredding" (Rose-John and Heinrich, 1996). The biological signals that induce shredding have yet to be identified. An alternative mechanism proposed for formation of the soluble form of IL-6R is differential splicing (Rose-John and Heinrich, 1996; Lust et al., 1992).

Both the soluble and membrane-bound forms of the IL-6R appear to be purely ligand-binding sites, with the signal-transduction capabilities arising from the binding of the IL-6R with a 130-kDa membrane glycoprotein referred to as gp130, a ubiquitously expressed transmembrane glycoprotein that is utilized by other members of this cytokine family (e.g., CNTF, LIF). Considerable information is available on the IL-6R/gp130 signal transduction pathway. However, most of this information comes from peripheral systems with little direct information derived from studies of CNS cells that express IL-6Rs. Thus, further studies will be needed to determine the extent to which CNS cells utilize the transduction pathways identified in peripheral cells.

The Kd for IL-6 binding to both the soluble and membrane-bound form of the IL-6R is approx 1–5 n*M*. IL-6 does not appear to have the

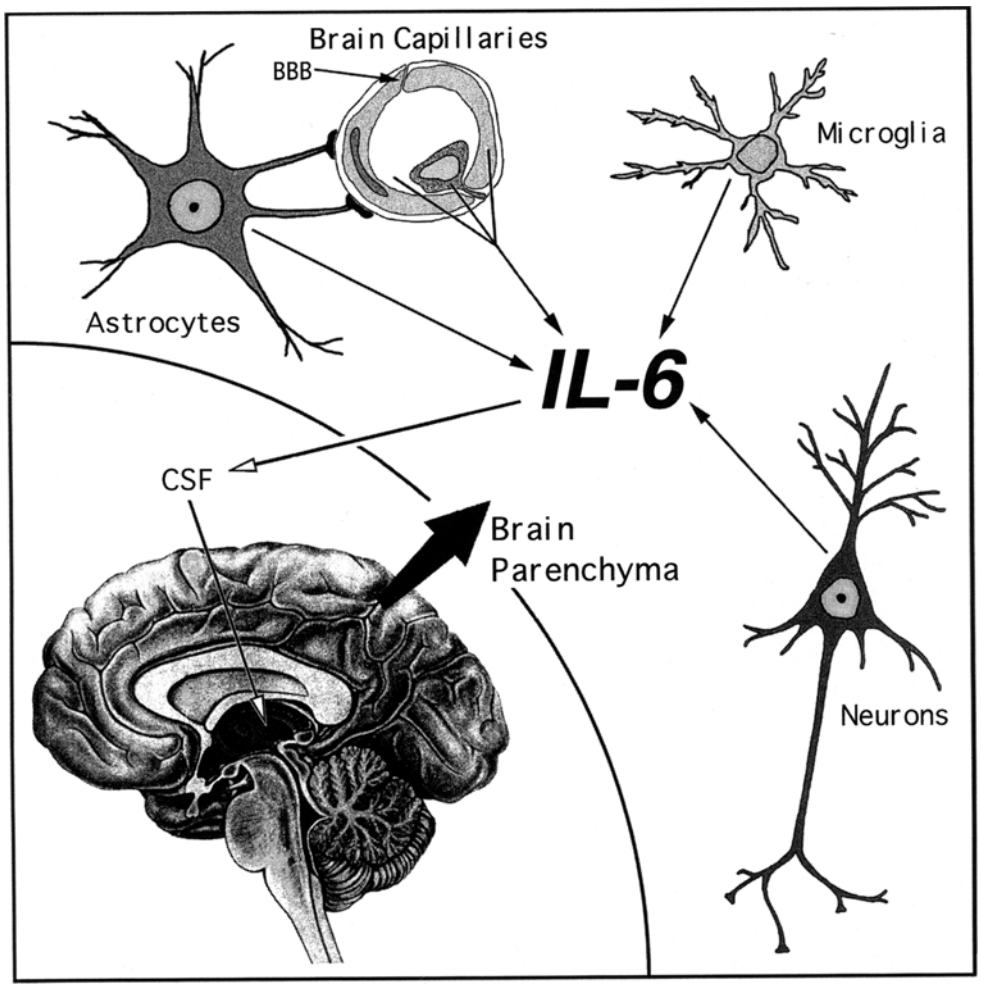

Fig. 1. Sites of IL-6 production and action within the CNS: IL-6 can be synthesized within the CNS by several types of cells of the brain parenchyma. Under normal conditions, some neurons and glia (astrocytes and oligodendrocytes) in various regions of the brain express IL-6 protein. Under pathological conditions, IL-6 levels in the CNS are elevated because of IL-6 production by activated microglia and astrocytes, by infiltrating macrophages and T-cells, and by endothelial cells of blood vessels in the brain. Moreover, circulating IL-6 may enter the brain after disease-related compromise of the blood–brain barrier (BBB). Elevated levels of IL-6 also occur in the cerebrospinal fluid (CSF) during a number of infectious diseases, neurological disorders, and brain trauma. Once synthesized and released, IL-6 may act on a variety of cell types in the CNS that express IL-6R, including neurons and glial cells. IL-6R is coexpressed with IL-6 in many regions of the CNS, and in some cases both IL-6 and IL-6R are synthesized within the same cell type, suggesting both an autocrine and paracrine mode of action for IL-6 in the CNS.

ability to bind directly to gp130. Binding of IL-6 to either the membrane-bound or soluble form of the IL-6R initiates an association of the receptor with gp130, followed by gp130 homodimerization, such that a complex comprised of IL-6 and IL-6R is covalently linked to two gp130s to form the signal-transduction unit (Fig. 2) (Taga et al., 1989; Murakami et al., 1993). The signal-transduction unit does not have intrinsic kinase activity, but associates with tyrosine kinases and is thought to induce their activation (Murakami et al., 1993; Stahl et al., 1994; Narazaki et al.,

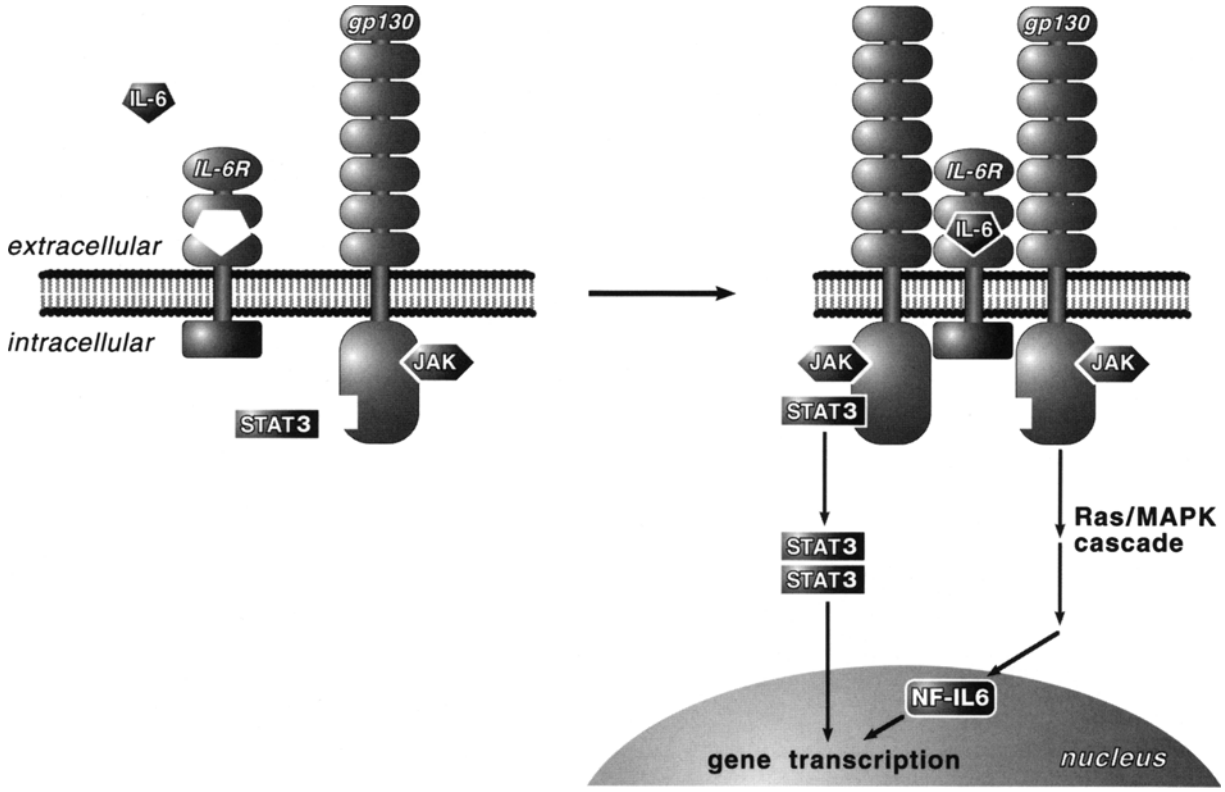

Fig. 2. IL-6 signal transduction involves the IL-6R and gp130. Binding of IL-6 to the IL-6R induces homodimerization of the gp130 subunit that leads to the activation of one of two pathways: The gp130 homodimer activates JAK tyrosine kinases that are associated with the gp130 molecules. JAK kinases can then tyrosine-phosphorylate gp130, facilitating the association of STAT3 with gp130. The JAK kinases then tyrosine-phosphorylate STAT3 on each gp130 molecule, thus enabling the release of STAT3 from gp130 and STAT3 homodimerization. The STAT3 homodimer then acts as a signal in the nucleus at the type 2 IL-6 response element to initiate gene transcription. Alternatively, the gp130 homodimer, through an unidentified mechanism, activates the RAS/MAPK cascade. The resulting phosphorylation of NF-IL6 by MAPK activates this nuclear factor allowing it to bind at the type 1 IL-6 response element in the nucleus to initiate gene transcription.

1994). Activation of the kinases leads to nuclear signaling via various transcription factors and the regulation of gene expression (Nakafuku et al., 1992; Satoh et al., 1992; Trautwein et al., 1993) (Fig. 2). More detailed information on the IL-6 signal transduction pathway can be found in several recent review articles on this topic (Kishimoto et al., 1992, 1995, 1994; Hibi et al., 1990; Miyajima et al., 1992; Taga and Kishimoto, 1992; Taga, 1996; Kishimoto, 1992; Stahl et al., 1995; Taniguchi et al., 1995; Akira et al., 1995).

The techniques available for detection of IL-6Rs in the CNS (e.g., assessment of IL-6R mRNA, immunodetection of IL-6R) cannot distinguish between membrane-bound and soluble forms of the receptor. Thus, although IL-6R has been localized to the CNS, it is not known if both soluble and membrane-bound forms are present, and if both are present, what the relative level of the two receptor forms is. Moreover, it is not known if the functional role of soluble IL-6R differs from that of the membrane-bound form in the CNS. For example, in addition to its role as an agonist, the soluble form could act as a functional antagonist under certain conditions. Thus, when present in excess of the membrane-bound form, the soluble form

could bind to IL-6, but not to the transduction subunit gp130. This would reduce the amount of IL-6 available for binding to the membrane-bound IL-6R and, consequently, limit activation of the gp130 signal-transduction pathway (Rose-John and Heinrich, 1996). Thus, the relative levels of soluble and bound forms of the IL-6R could be another important determinant of IL-6s actions in the CNS.

IL-6 Levels in the CNS

Whereas the studies cited above indicate that IL-6 and its receptor are expressed in the CNS, relatively little information is available on IL-6 levels in the CNS under physiological or pathological conditions. Several approaches have been used to assess IL-6 levels in the CNS parenchyma including: biochemical measurements of IL-6 in tissue samples or in microdialysates; a comparison of the relative degree of immunostaining for IL-6 utilizing antibodies specific for IL-6; and measurement of IL-6 mRNA levels under various conditions. Whereas these approaches provide valuable information about IL-6 levels in the CNS parenchyma, they are unable to provide information on IL-6 levels in the extracellular space adjacent to functional IL-6Rs. Without this information it is difficult to determine the range of IL-6 concentrations that can be considered physiologically relevant in the CNS or what the functional consequence of differing levels of IL-6 might be. Furthermore, without additional information, it is difficult to determine the relationship between the level of IL-6 mRNA and the level of active protein. Thus, inferences about the physiological or pathological relevance of various IL-6 levels in the CNS should be viewed with this caveat.

Measurement of IL-6 in the cerebrospinal fluid (CSF; Fig. 1) also provides information about IL-6 levels in the CNS. However, it is not clear how closely IL-6 levels in the CSF reflect IL-6 levels in the CNS parenchyma. Even so, information on CSF levels can contribute to an understanding of the physiological and pathological roles of IL-6 in the CNS. Moreover, IL-6 in the CSF could influence neurons and glia of the brain if diffusion from the CSF to the brain parenchyma occurs readily.

Another source of information on IL-6 levels in the CNS comes from studies of CNS cells in vitro. Culture-model systems have been used extensively to determine the ability of CNS cell types to produce IL-6. Culture systems have the advantage that cell types can be examined in isolation, a situation not possible in the intact CNS where numerous cell types are found in close association. Moreover, culture preparations offer the technical advantage that secreted IL-6 can be measured in the culture medium, facilitating quantification. Whereas studies of CNS cells in vitro do not provide direct information on IL-6 levels in the CNS, they do give some indication of the relative capability of different CNS-cell types to produce IL-6 under various conditions.

In biochemical studies, IL-6 levels are quantified by two methods: determination of IL-6 biological activity in samples (expressed as units/mL or U/mL) using bioassay systems; and/or determination of IL-6 protein (expressed as pg/mL or ng/mL) in samples using standard immunoassay methods (e.g., ELISA). Several different bioassay systems are available to assess IL-6 activity, however IL-6 activity (U/mL) in one bioassay may not be directly comparable to IL-6 activity measured in other bioassays that use different cell types or endpoints (e.g., cell proliferation). Protein measurements provide more standardized information, but the biological activity is unknown (unless measured independently with a bioassay) and different samples of equivalent IL-6 protein concentration may not have the same bioactivity. In spite of these limitations, determination of dose-response relationships (measured as bioactivity or protein concentration) is an important step in elucidating IL-6's physiological or pathological actions on various cell types in the CNS.

Results from studies utilizing the approaches outlined above indicate that IL-6 levels in the adult CNS (parenchyma and CSF) are low or undetectable under normal physiological con-

ditions. However, elevated levels occur as a common feature of injury, inflammation and CNS disease (Minami et al., 1991). A major source of IL-6 in these conditions is thought to be the astrocytes of the CNS (Fig. 1). Astrocytes are the most abundant cell type in the CNS and are known to provide structural and functional support to neurons (Eddleston and Mucke, 1993). As mentioned above, techniques to measure IL-6 production by astrocytes in the intact CNS are not currently available. However, studies in vitro have provided information on conditions under which IL-6 production occurs and the relative levels of IL-6 produced. Results from several recent studies are summarized in Table 1. Baseline levels of IL-6 production differ for various astrocyte preparations, as does the level of IL-6 production induced by various stimuli. Several factors are likely to account for this variability including culture conditions, the type and origin of the astrocytes, and the physiological state of the astrocyte. Measurement of IL-6 mRNA levels have shown that stimuli that induce increased synthesis of IL-6 in astrocytes also increase IL-6 mRNA levels (Sawada et al., 1993; Lafortune et al., 1996; Lee et al., 1993; Fiebich et al., 1996; Sawada et al., 1992; Lieberman et al., 1989; Kasahara et al., 1990).

IL-6 levels in supernatants from cultured human and rodent astrocytes are generally low or undetectable under baseline conditions, but increase dramatically when the astrocytes are stimulated with other cytokines or neuronal signaling molecules such as neurotransmitters. Interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) appear to be the most important cytokines in terms of the ability to induce IL-6 synthesis in astrocytes (Table 1). The effects of these cytokines are additive or synergistic when applied together (Benveniste et al., 1990). Neurotransmitters that have been reported to induce IL-6 production in astrocytes include norepinephrine (Maimone et al., 1993; Norris and Benveniste, 1993), substance P (Cadman et al., 1994), vasoactive intestinal peptide (Grimaldi et al., 1994) adenosine (Fiebich et al., 1996), and histamine (Cadman et al., 1994). There appears to be some species variation with respect to the ability of these neurotransmitters to induce IL-6 production in astrocytes (Table 1). Glutamate, the main excitatory transmitter in the CNS, does not influence IL-6 production in astrocytes (Maimone et al., 1993). The regulation of IL-6 production in astrocytes by neurotransmitters and cytokines may reflect a normal neuronal/glial communication pathway, since astrocytes are in close association with neurons at synaptic sites where neurotransmitters are released. Disruption of such a pathway may play an important role in the altered neuronal function characteristic of pathological conditions associated with elevated IL-6 levels in the CNS.

Injury or infection also results in increased production of IL-6 by astrocytes. Exposure to bacterial endotoxin (e.g., lipopolysaccharide; LPS, the active fragment of endotoxin from gram-negative bacteria) is often used experimentally to induce cellular changes that occur normally during infection and inflammation. LPS has been shown to increase IL-6 production by astrocytes in some studies (Table 1), consistent with a role for astrocytes in IL-6 production in pathological conditions.

Microglia are another important source of IL-6 in the CNS, especially during infection. Historically, microglia were considered to be derived from brain neuroepithelium, the tissue source of progenitor cells that differentiate into neurons and glial (e.g., astrocytes and oligodendrocytes) cells of the CNS. Based on their presumed origin, microglia were thought to represent another form of glial cell, thus accounting for the name. Whereas the origin of CNS microglia is still controversial, recent information indicates that the microglia are derived from the bone marrow and migrate to the CNS early in development (Hickey and Kimura, 1988) (*see* also reviews Thomas, 1992; Perry et al., 1993; Gehrmann et al., 1995). As such, microglia are now considered to be resident brain macrophages. Microglia are present throughout the gray and white matter of the CNS and thus are well situated to serve a regulatory role in the CNS (Giulian, 1987; Giulian and Baker, 1986). Studies in vitro have shown

Table 1
IL-6 Production by Various Cell Types In Vitro[a]

Cell type	Condition and/or stimulus	IL-6 levels	Reference
1. Astrocytoma (human)	Baseline control	0.4 ng/mL	(Cadman et al., 1994)
	Histamine (100 μ*M*)	13 ng/mL	
	Substance P (100 n*M*)	39 ng/mL	
	IL-1β (30 n*M*)	333 ng/mL	
2. Astrocytoma (human)	Baseline control	0.6 ng/mL	(Palma et al, 1994)
	Substance P (100 n*M*)	1.9 ng/mL	
3. Astrocytoma (human)	Baseline control	0	(Gitter et al., 1994)
	Substance P (100 n*M*)	3.5 ng/mL	
	IL-1β (50 pg/mL)	9 ng/mL	
4. Astrocytoma (human)	Baseline control	4 ng/mL	(Fiebich et al., 1996)
	Adenosine receptor agonist	60 ng/mL	
5. Fetal astrocytes (human)	Baseline control	<0.05 ng/mL	(Lee et al., 1993)
	IL-1β (20 U/mL)	0.9 ng/mL	
6. Fetal astrocytes (human)	Baseline control	0.1 ng/mL	(Aloisi et al., 1992)
	IL-1β (10 U/mL)	13 ng/mL	
	TNF-α (10 U/mL)	2.5 ng/mL	
	LPS (0.1 μg/mL)	0.16 ng/mL	
7. Adult astrocytes (human)	Baseline control	<5 U/mL	(Hariri et al., 1994)
	Trauma	50 U/mL	
8. Neonatal astrocytes (rat)	Baseline control	0.03 ng/mL	(Maimone et al., 1993)
	IL-1β (100 U/mL)	0.26 ng/mL	
	Norepinephrine (10 μ*M*)	0.26 ng/mL	
	Substance P (10 μ*M*)	0.06 ng/mL	
9. Neonatal cerebral astrocytes (rat)	Baseline control	102 U/mL	(Norris and Benveniste, 1993)
	IL-1β (2 ng/mL)	2385 U/mL	
	TNF-α (100 ng/mL)	2267 U/mL	
	Norepinephrine (10 μ*M*)	2485 U/mL	
	Norepinephrine (10 μ*M*) and IL-1β (2 ng/mL)	50,530 U/mL	
	Norepinephrine (10 μ*M*) and TNF-α (100 ng/mL)	44,400 U/mL	
	IL-1β (2 ng/mL) and TNF-α (100 ng/mL)	53,000 U/mL	

10. Neonatal cerebral astrocytes (rat)	Baseline control TGF-β (10 ng/mL) IL-1β (1 ng/mL) TNF-α (100 ng/mL) TNF-α (100 ng/mL) and TGF-β (10 ng/mL)	170 U/mL 1426 U/mL 3720 U/mL 990 U/mL 10,612 U/mL	(Benveniste et al., 1994)
11. Neonatal astrocytes (rat)	Hypoxia Reoxygenation	0.01 ng/mL 0.35 ng/mL	(Maeda et al., 1994)
12. Neonatal astrocytes (murine)	Baseline control IL-1β (20 U/mL) TNF-α (10^4 U/mL)	<10 U/mL 10,600 U/mL 4300 U/mL	(Frei et al., 1989)
13. Neonatal astrocytes (murine)	Baseline control TNF-α (50 U/mL) LPS (0.1 μg/mL)	<20 U/mL 150 U/mL 200 U/mL	(Sawada et al., 1992; Sawada et al., 1995)
14. Fetal telencephalic cells (rat)	Baseline control LPS (10 ng/mL)	5 U/mL 750 U/mL	(Romero et al., 1993)
15. TEV[b] infected astrocytes (murine)	TEV (10^5 PFU[c])	0.1 ng/mL	(Rubio and Sierra, 1993)
16. LCMV[d] infected astrocytes (murine)	Baseline control LCMV (10^5 PFU)	<10 U/mL 7680 U/mL	(Frei et al., 1989)
17. Fetal microglia (human)	Baseline control LPS (1 ng/mL)	0 15 ng/mL	(Lee et al., 1993)
18. Fetal microglia (human)	Baseline control LPS (10–15 μg/mL) IL-1α	99 U/mL 153 U/mL 851 U/mL	(Sebire et al., 1993)
19. Fetal microglia (human)	Baseline control IL-4 (200 U/mL) IL-13 (30 ng/mL)	1.2 ng/mL 2.7 ng/mL 5.0 ng/mL	(Sebire et al., 1996)
20. Microglia (30-d rats)	Baseline control LPS (5 μg/mL)	0 111 U/mL	(Woodroofe et al., 1991)
21. Microglia (rat)	Baseline control LPS (10–15 pg/mL)	0 2.4 ng/mL	(Gottschall et al., 1995)

(*continued*)

Table 1 *Continued*

Cell type	Condition and/or stimulus	IL-6 levels	Reference
22. LCMV[d] virus infected microglia (murine)	Baseline control	<10 U/mL	(Frei et al., 1989)
	LCMV (10^5 PFU)	23,040 U/mL	
23. Simian microglia	Baseline control	0.3 ng/mL	(Sopper et al., 1996)
	LPS (10 μg/mL)	4 ng/mL	
	SIV[e] infection in vitro	1 pg/mL	
	SIV infection in vitro and LPS (10 μg/mL)	8 ng/mL	
	SIV infection in vivo	0.5 ng/mL	
	SIV infection in vivo and LPS (10 μg/mL) in vitro	4 ng/mL	
24. Neonatal microglia (murine)	Baseline control	<10 U/mL	(Frei et al., 1989)
	IL-1β (20 U/mL)	55 U/mL	
	TNF-α (10^4 U/mL)	67 U/mL	
25. Neonatal microglia (murine)	Baseline control	<5 U/mL	(Suzumura et al., 1996)
	GM-CSF[f] (100 U/mL)	340 U/mL	
26. Embryonic cortical neurons	Baseline control	0.02 ng/mL	(Ringheim et al., 1995)
	IL-1β (0.1 n*M*)	0.16 ng/mL	
	TNF-α (1 n*M*)	0.23 ng/mL	
	IL-1β (0.1 n*M*) and TNF-α (1 n*M*)	1.1 ng/mL	

[a] Mean values in culture medium.
[b] Theiler's encephalomyelitis virus.
[c] Plaque-forming units.
[d] Lymphocytic choriomeningitis virus.
[e] Simian immunodeficiency virus.
[f] Granulocyte/macrophage colony-stimulating factor.

that microglia, like astrocytes, produce low levels of IL-6 under baseline conditions, but synthesize relatively large quantities of IL-6 when activated by various factors. LPS is one of the most effective inducers of IL-6 synthesis in microglia. Table 1 summarizes some of the recent data on this topic. IL-6 mRNA is detected in stimulated microglia (Sawada et al., 1993; Lafortune et al., 1996; Sawada et al., 1992; Righi et al., 1989; Sebire et al., 1993; Yamabe et al., 1994; Walker et al., 1995) consistent with the biochemical data showing IL-6 production by this CNS cell type.

Other sources of IL-6 in the CNS include endothelial cells of the vascular system (Fabry et al., 1993), infiltrating mononuclear blood cells such as T-cells and macrophages that are a major source of IL-6 during injury and inflammation (Benveniste, 1992), and passive transfer from the serum. Under normal conditions, diffusion of blood-borne macromolecules to the CNS and migration of immune cells from the blood to the CNS is regulated by tight intercellular junctions between adjacent endothelial cells of the vasculature. These tight junctions are a major component of the blood–brain barrier (BBB) (Fig. 1). However, when the BBB is compromised, as occurs in certain disease states (e.g., HIV infection), serum cytokines can gain access to the CNS. Endothelial cells of the BBB are an additional source of IL-6 when cytokines (e.g., IL-1β) or other agents (e.g., viral proteins) induce IL-6 production in these cells (Rott et al., 1993). However, passive transfer of IL-6 across the BBB appears to be negligible under most conditions, since CSF levels of IL-6 typically do not correlate with plasma levels of IL-6. Thus, serum levels of IL-6 are often low under pathological conditions that induce high IL-6 levels in the CSF (Table 2). In these cases, elevated levels of IL-6 in the CSF are likely to be because of IL-6 production by infiltrating T-cells and macrophages, as well as from IL-6 production by brain parenchyma cells.

Neurons and oligodendrocytes also contribute to IL-6 levels in the CNS under some conditions. Embryonic CNS neurons studied in culture produce IL-6 mRNA and protein when stimulated with the cytokines IL-1β and TNF-α, an effect that is synergistic when the cultures are exposed simultaneously to both cytokines (Ringheim et al., 1995). A synergistic effect of IL-1β and TNF-α on IL-6 production in astrocytes has also been noted (Benveniste et al., 1990). In vitro studies have also shown that oligodendrocytes (glial cells responsible for myelination of axons in the CNS) express IL-6 mRNA when infected with measles virus (Yamabe et al., 1994), suggesting a contribution of this cell type to IL-6 levels in the CNS during infection. However, further studies demonstrating IL-6 protein expression by oligodendrocytes will be needed to confirm this role. Thus, it appears that numerous cell types within the CNS are capable of producing IL-6 and may play a role in the physiological or pathological effects of IL-6 in the CNS.

Biosynthesis and Release of IL-6

As noted above, IL-6 levels in the CNS are low or undetectable under baseline physiological conditions, suggesting that relatively little constitutive biosynthesis occurs. Injury, inflammation, and CNS disease triggers increased IL-6 gene expression and protein synthesis (Table 1). Also as noted above, numerous cell types in the CNS are capable of IL-6 synthesis, especially after stimulation by appropriate factors. The relative potency of the various stimulatory factors to induce IL-6 production is dependent on cell type. For example, in astrocytes IL-1β and TNF-α are important inducers of IL-6 gene expression (Frei et al., 1989; Benveniste et al., 1994; Lieb et al., 1996) and consequently IL-6 production, whereas viral proteins appear to be more potent inducers of IL-6 production in microglia (Table 1). Intracellular second messengers such as cAMP and protein kinase C (PKC) and transcription factors such as NF-κB and AP-1 have been shown to play a role in the regulation of IL-6 gene expression (Lieb et al., 1996; Norris et al., 1994). Detailed information on this topic is available in several recent reviews (Akira and

Table 2
IL-6 Levels in the Brain or CSF under Various Conditions[a]

Condition	Subject	CSF	Brain homogenate	Sera	Reference
1. Experimental autoimmune encephalomyelitis (EAE; murine)	Control EAE	30 U/mL 8000 U/mL	1.9 log 10 U/gwtw[b] 3.0 log 10 U/gwtw	10 U/mL 50 U/mL	(Gijbels et al., 1990)
2. Theiler's encephalomyelitis virus infection (murine)	Control Experimental	nd[c] nd	0 ng/mL 0.6 ng/mL	0 0	(Rubio and Sierra, 1993)
3. Lymphocytic chorio-meningitis virus (LCMV; murine)	Control LCMV (100 PFU[d])	<10 U/mL 100,000 U/mL	nd nd	50 U/mL 100U/mL	(Frei et al., 1989)
4. Retroviral infection (murine)	Control Leukemia virus	nd nd	0 ng/mL 0.05 ng/0.1 mg	nd nd	(Nagra et al., 1994)
5. Experimental meningitis (rabbit)	Control Meningococcal LPS	0 0.15 ng/mL	nd nd	nd nd	(Waage et al., 1989)
6. Transient cerebral ischemia hippocampus (gerbil)	Control Experimental	nd nd	0 ng/mL 0.05 ng/mL	nd nd	(Saito et al., 1996)
7. Ischemia/reperfusion hippocampus (rat)	Control Experimental	0.04 ng/mg protein 0.09 ng/mg protein	nd nd	nd nd	(Maeda et al., 1994)
8. Mechanical injury (microdialysis probe; rat)	Control Probe implantation-d 0[e] Probe implantation-d 1 Probe implantation-d 2	<0.005 U/mL[f] 0.11 U/mL[f] 0.15 U/mL[f] <0.01 U/mL[f]	0 1.15 U/mL[g] 1.30 U/mL[g] 0.40 U/mL[g]	nd nd nd nd	(Woodroofe et al., 1991)
9. Mechanical injury (microdialysis probe; rat)	Control striatum Probe implantation-d 0[e]	<1U/μL 2184 U/840 μL[h]	nd nd	nd nd	(Yan et al., 1992)
10. Traumatic brain injury (TBI; rats)	Control TBI	nd nd	<2 U/mg protein 350 U/mg protein	<10 U/mL 120 U/mL	(Taupin et al., 1993)
10. Stroke patients (humans)	Control d 0 d 2	nd 0.050 ng/mL 0.338 ng/mL	nd nd nd	nd 0.050 ng/mL 0.073 ng/mL	(Tarkowski et al., 1995)
11. Sudden infant death syndrome (SIDS; humans)	Violent death SIDS Infection	0 0.007 ng/mL 0.040 ng/mL	nd nd nd	nd nd nd	(Vege et al., 1995)

12. Parkinson's disease (humans)	Control caudate and putamen	0.002 ng/mL	nd	nd	(Mogi et al., 1994)
	Parkinson caudate and putamen	0.023 ng/mL	nd	nd	
13. Subarachnoid hemorrhage (SAH; humans)	Control	0.041 ng/mL	nd	0.008 ng/mL	(Mathieson et al., 1993)
	SAH	2.0 ng/mL	nd	<0.024 ng/mL	
14. Traumatic brain injury (TBI; humans)	Control	nd	nd	nd	(Kossmann et al., 1995, 1996)
	TBI d 1[e]	1.2 ng/mL	nd	0.09 ng/mL	
	TBI d 14	0.1 ng/mL	nd	0.04 ng/mL	
15. Infection (humans)	Control[i]	<0.07 ng/mL	nd	nd	(Waage et al., 1989)
	meningitis	154 ng/mL	nd	nd	
	Septic shock/bacteremia	42 ng/mL	nd	nd	
16. Infection (humans)	Control	<10 U/mL	nd	0 U/mL	(Houssiau et al., 1988)
	Herpes simplex encephalitis	10–100 U/mL	nd	0 U/mL	
	Meningitis	100–1000 U/mL	nd	0 U/mL	
17. Infection—pediatric patients (human)	Control	<0.005 ng/mL	nd	nd	(Matsuzono et al., 1995)
	Bacterial meningitis	50 ng/mL	nd	14 ng/mL	
	Aseptic meningitis	1.0 ng/mL	nd	<0.100 ng/mL	
	Encephalitis	0.4 ng/mL	nd	<0.100 ng/mL	
18. Infection (humans)	Control	0.57 ng/mL	nd	0.43 ng/mL	(Eddleston and Mucke, 1993)
	Purulent bacterial meningitis	6.60 ng/mL	nd	nd	
	Aseptic meningitis	2.20 ng/mL	nd	0.36 ng/mL	
	Lymphocytic bacterial meningitis	0.80 ng/mL	nd	nd	

[a] All values are means or medians.
[b] gwtw = gram wet tissue weight.
[c] nd = not determined.
[d] PFU = plaque-forming units.
[e] d 0 = day of injury.
[f] 1 unit = 200 pg human IL-6.
[g] Measurement of brain dialysate.
[h] Reflects only 1% of the extracellular concentration, recovery tests indicate that recovery was 3.4%.
[i] Patients with nonbacterial neurological diseases.

Kishimoto, 1992; Akira et al., 1995; Benveniste et al., 1995).

IL-6 mRNA is considered to be derived from a single gene (Yamasaki et al., 1988). Like most glycoproteins, IL-6 is synthesized from mRNA in the rough endoplasmic reticulum and processed for secretion according to the classical pathway used for peptides containing an N-terminal hydrophobic signal sequence. This pathway involves processing of the precursor protein in the Golgi apparatus, accumulation of the protein in secretory granules, and release of the mature proteins to the extracellular space by fusion of the granules with the cellular membrane (Schobitz et al., 1994; Boyd and Beckwith, 1990). IL-6 presumably diffuses to target cells expressing IL-6R or may act in an autocrine fashion for cells that express both IL-6 and IL-6R. The action of IL-6 is eventually terminated by internalization after membrane binding (Nesbit and Fuller, 1992).

Role of IL-6 in CNS Physiology and Pathology

The functional roles of IL-6 in the CNS have yet to be defined unambiguously. However, numerous studies indicate that IL-6 is involved in both physiological and pathological processes in the CNS, as summarized below.

Effects of IL-6 on the HPA (Hypothalamic-Pituitary-Adrenal) Axis

Increased levels of adrenocorticotropin hormone (ACTH) and glucocorticoids are observed in the circulation in many diseases, suggesting that activation of the HPA axis is an important component of the immune response (Dunn and Wang, 1995; Besedovsky et al., 1995). Cytokines have been implicated as a link between the immune, nervous, and endocrine systems, and thus may play a role in the activation and regulation of the HPA axis. For example, IL-6 (and IL-1), when injected systemically into rodents or humans (Dunn and Wang, 1995; Naitoh et al., 1988; Perlstein et al., 1991; Harbuz et al., 1992; Mastorakos et al., 1993; Stouthard et al., 1995) as well as intracerebroventricularly in rodents (Matta et al., 1992), has been shown to induce elevations in ACTH (released from the anterior pituitary), as well as corticosterone and cortisol (produced by the adrenal cortex in response to ACTH). Moreover, administration of antibodies against IL-6 can abolish the ACTH production induced by the bacterial endotoxin LPS (Perlstein et al., 1993).

Several lines of evidence indicate that an important CNS site of action for IL-6 in HPA activation is the paraventricular nucleus (PVN) of the hypothalamus, which contains corticotropin-releasing factor (CRF)-containing neurons that trigger the release of ACTH from the pituitary. For example, IL-6 has been shown to induce rapid and significant elevations in CRF release from explants of rat hypothalamus (Navarra et al., 1991). Stimulation of CRF release in these studies was selective for IL-6 and IL-1, whereas other cytokines such as IL-2, IL-8, TNF, interferon-α_2, and interferon-γ failed to induce CRF release from the hypothalamic explants. Other studies showed that the primary site of IL-6's actions in the HPA axis is above the level of both the pituitary and the median eminence, i.e., at the PVN. For example, in isolated median eminence, the site of CRF release from axon terminals of PVN neurons, no elevation of CRF was observed in response to IL-6 application (Navarra et al., 1991). Likewise, isolated anterior pituitary cells do not secrete ACTH in response to IL-6 treatment (Navarra et al., 1991). However, prolonged IL-6 exposure of isolated anterior pituitary cells can lead to enhanced ACTH release, although this effect occurs on a much longer timescale than what is known to occur for IL-6 stimulation of ACTH production in vivo (Naitoh et al., 1988; Navarra et al., 1991).

Prolonged IL-6 exposure in vitro also induces the release of other anterior pituitary hormones, such as growth hormone, follicle-stimulating hormone, luteinizing hormone, and prolactin (Yamaguchi et al., 1990; Spangelo et al., 1989). IL-6 might also play a role in stimulating the release of the posterior pituitary hormones vasopressin and oxytocin (Yasin et al., 1994). The

release of both of these hormones from hypothalamic explants is inducible by IL-6 (and IL-1β) exposure (Yasin et al., 1994). The primary function of vasopressin is to stimulate the resorption of water by the kidneys. However, there is currently no link between IL-6 and the regulation of renal function. Vasopressin can also act at the level of the median eminence (along with CRF) to release ACTH from the anterior pituitary (Gillies et al., 1982; Liu et al., 1990; Holmes et al., 1986; Vandesande, et al., 1977; Tramu et al., 1983). Thus, IL-6 may act via both the CRF and vasopressin systems to regulate ACTH release. Oxytocin is involved in parturition and stimulation of its release by IL-6 might thus be involved the induction of preterm labor caused by amniotic infections (Mc Duffie et al., 1992; Romero et al., 1991, 1989). The stimulatory effects of IL-6 (and IL-1) on the release of pituitary hormones are blocked by the cyclooxygenase inhibitors indomethacin and ibuprofen, but not by lipoxygenase inhibitors, suggesting that the formation of prostaglandins is an essential step in these neuroendocrine processes (Navarra et al., 1991; Yasin et al., 1994). The pathway for production of cyclooxygenase products by IL-6 has not been elucidated.

Whereas the effects of IL-6 in the hypothalamus could be caused by IL-6 produced outside the CNS, there is now evidence that IL-6 is produced locally within the hypothalamus. Release of IL-6 can be detected in in vitro hypothalamic preparations after stimulation with agents such as LPS, cAMP analogs, IL-1β, TNF, or estradiol (Spangelo et al., 1990a; Yamaguchi et al., 1990). In addition, synthesis of IL-6 mRNA can be induced by cAMP analogs (Spangelo et al., 1990a). However, the use of high K^+ media to depolarize the neurons does not induce IL-6 release, suggesting that the release of IL-6 in the hypothalamus is depolarization-independent and that the source of IL-6 within the hypothalamus is nonneuronal (Spangelo et al., 1990a). In addition, in vitro experiments have shown that the anterior pituitary is a site of IL-6 release as well as a site of IL-6 action (Spangelo et al., 1990b). In the anterior pituitary, IL-6 is expressed by glia-like support cells known as folliculo-stellate cells (Vankelcom et al., 1989). Production of IL-6 in the pituitary is stimulated by elevations in cAMP levels (Spangelo et al., 1990; Carmeliet et al., 1991) and is under negative feedback control from glucocorticoids (Carmeliet et al., 1991).

A role of IL-6 and other cytokines in the activation of various components of the stress-response system in the CNS has been implicated as well. Systemic injections of IL-6 stimulate the production of the noradrenergic catabolite 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) in the hypothalamus (Dunn and Wang, 1995), the dopaminergic catabolite dihydroxyphenylacetic acid (DOPAC) in the prefrontal cortex (Zalcman et al., 1994), and both the serotonin precursor tryptophan in the hypothalamus, hippocampus, and brain stem, and the serotonin catabolite 5-hydroxyindoleacetic acid (5-HIAA) in the prefrontal cortex and brain stem (Dunn and Wang, 1995). These monoaminergic systems are known to be highly active during infectious diseases (Dunn et al., 1989). Thus, cytokines produced during the immune response to infection could play a role in the activation of the stress-response system in the CNS through activation of central monoaminergic pathways as well as by stimulation of the adrenal cortex via HPA activation.

Role of IL-6 in Fever

Fever is common to a number of infectious diseases (e.g., AIDS, and viral and bacterial infections) that are associated with increased plasma levels of IL-6 (Luheshi and Rothwell, 1996). Indeed, there is a strong correlation between the induction of fever and IL-6 levels in plasma (Hopkins and Rothwell, 1995; Luheshi and Rothwell, 1996) and in the CNS (LeMay et al., 1990) (for reviews see LeMay et al., 1990; Roth et al., 1993). Systemic injection of LPS results in fever production as well as an elevation of IL-6 within the CNS (Roth et al., 1993; Klir et al., 1993; LeMay et al., 1990) and plasma (Roth et al., 1993; LeMay et al., 1990a,b). Also, IL-6 injected systemically (Blatteis et al., 1990; Rothwell et al., 1991; Dinarello et al., 1991), intracerebroventricularly (Roth et al., 1993;

Rothwell et al., 1991; Dinarello et al., 1991; Opp et al., 1989; Strijbos et al., 1992), or infused directly into the preoptic area (POA) of the hypothalamus (Blatteis et al., 1990; Lesnikov et al., 1991) has been shown to elicit fever in a number of animal models. Antibodies against IL-6 inhibit fever induced by peripheral injection of LPS or by central administration of IL-1, another pyrogenic (i.e., fever-producing) cytokine (Rothwell et al., 1991). The pyrogenic effects of IL-6 and LPS are blocked by cyclooxygenase inhibitors such as indomethacin or ibuprofen, indicating the involvement of prostaglandins in IL-6-induced fever (LeMay et al., 1990; Blatteis et al., 1990; Dinarello et al., 1991; Strijbos et al., 1992; Blatteis et al., 1991). Interestingly, the opioid antagonist naloxone also reduces IL-6-mediated fever (Blatteis et al., 1991). Because injection of β-endorphin, morphine, and other opioids can induce fever (Xin and Blatteis, 1992; Rothwell, 1994; Rothwell et al., 1991), these results suggest the involvement of opioids in fever production by IL-6.

Another approach to studying the involvement of IL-6 in fever is through the use of transgenic mice. IL-6-deficient mice fail to produce fever following systemic injection of LPS or central or peripheral administration of IL-1β, although central injection of IL-6 does induce a fever response in these transgenic mice (Chai et al., 1996). These data suggest that both LPS and IL-1β-mediated fever is dependent on expression of IL-6 in the CNS (Chai et al., 1996). This relationship between IL-1β and IL-6 is further supported by the inhibition of both LPS-induced fever and CNS (hypothalamic) IL-6 elevation via the administration of an IL-1-neutralizing antibody or IL-1-receptor antagonist (LeMay et al., 1990a; Luheshi et al., 1996; Klir et al., 1994).

One possible mechanism for fever induction by IL-6 in the CNS is via the release of CRF, which also mediates the thermogenic (i.e., heat-producing) responses to several other pyrogenic neurochemicals (Luheshi and Rothwell, 1996; Rothwell, 1994). Although the site(s) of CRF action in thermogenic responses has yet to be determined (Rothwell, 1994), blockade of CRF's actions in the CNS prevents the induction of fever by IL-6 (Strijbos et al., 1992; Rothwell, 1994). As mentioned above, IL-6 can stimulate production of CRF in the PVN of the hypothalamus. However, the pyrogenic actions of CRF do not appear to involve release of hormones (i.e., ACTH) from the anterior pituitary, but rather the synthesis of other proopiomelanocortin products (such as β-endorphin and γ-melanocyte-stimulating hormone) within the CNS (Rothwell et al., 1991). It has been hypothesized that CRF-mediated fever responses are produced via activation of the sympathetic nervous system and consequent thermogenic processes involving metabolic rate, rather than by an adjustment by CRF of the thermoregulatory integrative mechanisms within the POA that determine the set-point body temperature (Rothwell, 1994).

In contrast to the view that IL-6-induced fever is mediated by CRF, IL-6 may induce fever directly. Consistent with this possibility, IL-6 has been shown to alter the activity of thermosensitive neurons in the POA of the hypothalamus. Thermosensitive neurons normally function as homeostatic regulators of body temperature. As such, they ensure that changes in body temperature result in appropriate physiologic responses to either produce or reduce heat. IL-6 suppresses the spontaneous firing rate of warm-sensitive neurons (neurons that respond to increased body temperature with an increase in firing rate), and increasing the spontaneous firing rate of cold-sensitive neurons (decreased body temperature activates these neurons) in the POA in hypothalamic slice preparations (Xin and Blatteis, 1992). These effects of IL-6 on thermosensitive neurons are consistent with a role of IL-6 as an endogenous pyrogen, because an IL-6-mediated reduction in the firing rate of warm-sensitive neurons and an increase in the firing rate of cold-sensitive neurons would result in physiologic responses that produce heat, thus leading to fever induction. As was shown for the pyrogenic effects of IL-6 in vivo, the effects of IL-6 on the neuronal activity in the POA in vitro are blocked by cyclooxygenase inhibitors (indomethacin) or

opioid antagonists (naloxone) (Xin and Blatteis, 1992). IL-6's regulation of the spontaneous activity of POA-thermosensitive neurons is one of only a few examples of a direct effect of cytokines on the firing activity of CNS neurons, although this aspect of cytokine actions in the CNS has been relatively unexplored.

Whereas it is clear that cyclooxygenase products are crucial for the IL-6-mediated fever response, the involvement of specific prostaglandins is less clear. PGE_2 is known to mediate the actions of several pyrogens in the CNS and blood (Rotondo et al., 1988; Milton, 1989; Blatteis, 1988). However, fever responses induced by PGE_2 are not inhibited by blocking the actions of CRF (Rothwell, 1990), a manipulation that prevents induction of fever by IL-6 (Strijbos et al., 1992; Rothwell, 1994). Moreover, IL-6 does not induce PGE_2 release in the hypothalamus in vitro (Dinarello, 1989). IL-6-induced fevers might be dependent on $PGF_{2\alpha}$ production rather than $PGE_{2\alpha}$ production, since fever responses induced by $PGE_{2\alpha}$ are inhibited by blocking the actions of CRF (Rothwell, 1990). Further studies are necessary to elucidate the precise mechanisms by which IL-6 induces fever.

Role of IL-6 in Neuronal and Glial Differentiation and Survival

Another action of IL-6 that has been studied extensively is its trophic effect on neurons. IL-6, like nerve growth factor (NGF), can induce the differentiation of PC12 cells into sympathetic-like neurons. The differentiation process is characterized by the transformation of morphologically undifferentiated round cells into cells possessing long neurites, and the concomitant expression of [^{3}H] saxitoxin-binding, indicative of the presence of voltage-dependent Na^+ channels responsible for neuronal excitability (Satoh et al., 1988). In addition, IL-6 supports the short-term survival (up to approx 10 d) of PC12 cells under adverse conditions, such as in growth medium that lacks NGF and serum, a condition that normally kills the cells (Satoh et al., 1988; Umegaki et al., 1996), or after addition of a calcium ionophore to the culture medium, which is also lethal (Umegaki et al., 1996). IL-6 induces a transient upregulation of the proto-oncogene c-*fos* in PC-12 cells (Satoh et al., 1988), an effect also observed for NGF. Interestingly, both IL-6- and NGF-mediated survival of PC12 cells is independent of protein synthesis, because cycloheximide (an inhibitor of protein synthesis) does not block their trophic effects (Umegaki et al., 1996). IL-6 does block DNA fragmentation in PC12 cells, which normally occurs during the apoptotic pathway of cell death, suggesting that IL-6's trophic actions are caused by the prevention of apoptosis (Umegaki et al., 1996).

IL-6 has also been shown to support the survival of mature, differentiated neurons in vitro. For example, significantly higher numbers of mature, cultured, septal-cholinergic neurons survive in the presence of IL-6 than under control conditions, as evidenced by increased choline acteyltransferase (ChAT) activity and number of acetylcholinesterase (AChE)-immunostained neurons (Hama et al., 1989, 1991) in IL-6-treated cultures. Although IL-6 can induce the release of NGF from astrocytes in culture (Frei et al., 1989), this is not the mechanism responsible for the IL-6-mediated trophic effects on septal neurons, because removal of the astrocytic feeder layer does not block the trophic actions of IL-6 (Hama et al., 1989). Moreover, IL-6 and NGF act synergistically to promote cell survival (Hama et al., 1989, 1991). However, unlike NGF, IL-6 does not induce the differentiation or survival of septal cholinergic neurons at embryonic stages of development (Hama et al., 1989). Thus, the mechanisms of IL-6's and NGF's trophic effects may be somewhat different.

Another group of CNS neuron that exhibit sensitivity to the trophic actions of IL-6 are the mesencephalic (midbrain) catecholaminergic neurons that immunostain for tyrosine hydroxylase (TH) (Hama et al., 1989; Kushima et al., 1992; Akenaya et al., 1995). IL-6 increases the number of mature, TH-immunoreactive midbrain neurons surviving in culture, and enhances their morphological development (Hama et al., 1991; Kushima et al., 1992). This effect appears to be

specific to catecholaminergic neurons, as IL-6 significantly elevates the amount of norepinephrine and especially dopamine in the cultures (measured by HPLC), and the relative increase in surviving TH-positive neurons is greater than the relative increase in the total number of neurons (identified by immunostaining with an antibody to MAP-2) (Hama et al., 1991; Kushima et al., 1992). IL-6 also has toxic effects on these neurons during the early culture period. Thus, compared to control cultures, the number of surviving neurons is reduced when IL-6 is present prior to 2 d in vitro (Kushima et al., 1992). After 2 d in vitro, IL-6 enhances the survival of the neurons as noted above. The effect of IL-6 on the survival of midbrain neurons appears to be age dependent, because cultured embryonic midbrain neurons exhibit a different dose dependency to IL-6 than that observed for the cultured postnatal neurons (Hama et al., 1991; Kushima et al., 1992). In cultures of embryonic neurons, only low doses of IL-6 show survival-promoting actions on TH-immunoreactive neurons, and the increase in number of surviving neurons is smaller than that observed for the postnatal, cultured TH-immunoreactive neurons (Hama et al., 1991).

Although IL-6 does not appear to play a prominent role in the early development of catecholaminergic neurons, it has been shown to protect these neurons from neurotoxicity induced by the compound 1-methyl-4-phenylpyridinium (MPP+), which is used experimentally to model the loss of dopaminergic neurons in Parkinson's disease (Akaneya et al., 1995). Another cause of neurotoxicity in the CNS is the excessive activation of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor. Because NMDA receptors are permeable to calcium, excessive activation can lead to an elevation in the level of cytosolic calcium, and consequently activation of several injurious intracellular cascades that ultimately lead to neuronal death (Choi, 1988; Rothman and Olney, 1995). Injection of IL-6 into the striatum was found to selectively protect cholinergic but not GABAergic neurons (as measured by relative amounts of ChAT and glutamic acid decarboxylase activity, respectively) from excitotoxicity induced by injection of NMDA (Toulmond et al., 1992). IL-6 also prevents NMDA receptor-mediated neurotoxicity in cultured hippocampal neurons (Yamada and Hatanaka, 1994). However, in cultured cortical neurons, IL-6 failed to reduce the glutamate-induced release of lactate dehydrogenase (LDH), a marker for neurotoxicity (Toulmond et al., 1992). The differential sensitivity of hippocampal and cortical cultures to IL-6's neuroprotective effects apparently relates to the neuronal types present in culture, since the cortical cultures were shown to contain a large proportion of GABAergic neurons, a neuronal type resistant to the neuroprotective effects of IL-6 (Toulmond et al., 1992).

In addition to these actions of IL-6 on cell survival, growth, and development, recent studies from our laboratory have shown that IL-6 can alter the neuronal response to NMDA receptor activation. In our studies, chronic treatment of cultured cerebellar-granule neurons with IL-6 at a dose (5 ng/mL) that induces trophic effects in other neuronal types (range in other studies is 0.1–50 ng/mL) enhanced the intracellular calcium response (i.e., calcium signal) elicited by brief (s) application of NMDA (Qiu et al., 1995) or glutamate (Holliday et al., 1995) to the granule neurons. IL-6's effects were selective for the response to NMDA, as IL-6 treatment did not alter the intracellular calcium signal elicited by similar application of domoate (an agonist at the kainate subtype of glutamate receptor) or by K^+ depolarization. Moreover, electrophysiological studies showed that IL-6 treatment increased the membrane and current response to NMDA, effects that are indicative of an increase in NMDA receptor number or a change in NMDA receptor function (Qiu et al., 1997). These changes in electrophysiological parameters could explain the enhanced calcium signal to NMDA, since a larger current response to NMDA is likely to result in greater calcium influx through the NMDA receptors. Calcium is an important intracellular messenger and the IL-6-induced increase in intracellular calcium levels during NMDA-receptor activation could

have important physiological or pathological consequences to these neurons. For example, additional studies showed that IL-6 treatment enhanced NMDA-induced neurotoxicity and cell death in the granule neurons, perhaps due to IL-6's effects on intracellular calcium levels (Qiu et al., 1997).

Thus, studies to date indicate that IL-6 can have both neurotrophic and neurotoxic effects on CNS neurons, although the mechanisms mediating these effects have yet to be fully elucidated. These divergent effects of IL-6 may relate to the different neuronal types studied, the developmental stages of the neurons under study, the duration or method of IL-6 application, and the dose of IL-6 tested (especially in terms of its specific activity; i.e., in U/mL). More extensive investigation of IL-6's actions on CNS neurons at the cellular and molecular levels will be necessary for a clearer understanding of these divergent effects of IL-6.

In addition to its trophic actions on neurons, IL-6 has been reported to exert trophic effects on glial cells, and particularly oligodendrocytes. For example, IL-6 treatment of cultured oligodendrocytes from rat optic nerve promotes oligodendrocyte survival on a short-term basis (Barres et al., 1993). However, the presence of other factors from other trophic classes (e.g., insulin-like growth factors and neurotrophins) appears to be necessary for more long-term survival (Barres et al., 1993). IL-6 can also influence glial cell differentiation in rat cortical cultures (Kahn and De Vellis, 1994). For example, when added to the culture medium of oligodendrocyte-progenitor cells of the CG-4 cell line, IL-6 induces an increased expression of glial fibrillary-acidic protein (GFAP) mRNA and protein, indicating a developmental progression of these cells along a type-2 astrocyte lineage (Kahn and De Vellis 1994). However, the role of IL-6 in glial differentiation is still unclear. IL-6 mRNA is not found by RT-PCR in mixed glial cultures of newborn mouse brain unless the glial cells are stimulated with LPS, nor is IL-6 mRNA present in the cerebral cortex during postnatal development of mice (Mizuno et al., 1994).

Studies with Transgenic Mice Overexpressing IL-6

Whereas the effects of IL-6 under physiological conditions have received much attention, relatively little is known about the effects of this cytokine under pathological conditions. IL-6 is known to be released in the CNS during various pathological conditions and has been hypothesized to serve a protective function. However it is now apparent that dysregulation of IL-6 production may be a contributing factor to the neuropathology and pathophysiology associated with many diseases. Much of what is known about the pathological effects of IL-6 has come from studies utilizing transgenic murine models of IL-6 expression in the CNS. Two different approaches have been used to construct transgenic mice for these studies: expression of human IL-6 by CNS neurons under the control of the rat neuron-specific enolase promoter (NSE-IL6 mice) (Fattori et al., 1995); and expression of murine IL-6 by astrocytes under the control of the murine glial fibrillary-acidic protein promoter (GFAP-IL6 mice) (Campbell et al., 1993).

In the NSE-IL6 model of IL-6 overexpression, reactive gliosis is found throughout the brain as evidenced by increased size and numbers of GFAP-positive astrocytes and ramified microglia (Fattori et al., 1995). However, no overt pathologies in neuronal populations, CNS vascularization, or behavior are found in this transgenic model (Fattori et al., 1995). In addition, the NSE-IL6 transgenic mice produce elevated levels (compared to control mice) of the inflammatory cytokines IL-1β, IL-6, and TNF in the CNS, but not in the periphery, after systemic or central LPS injection (Di Santo et al., 1996). The elevated levels of inflammatory cytokines in the CNS of the transgenic mice is consistent with the increased numbers of astrocytes and microglia, cell types that are responsible for cytokine production within the CNS in response to LPS.

The GFAP-IL6 transgenic model also exhibits reactive gliosis throughout the CNS (Campbell et al., 1993; Chiang et al., 1994). The gliosis in

these mice is characterized by elevated expression of GFAP mRNA and protein as well as hypertrophy of astrocytes (Campbell et al., 1993; Chiang et al., 1994). In contrast to the NSE-IL6 model, severe neuronal and vascular pathology is present in the GFAP-IL6 mice and these mice also exhibit behavioral abnormalities (Campbell et al., 1993; Chiang et al., 1994; Brett et al., 1996; Steffenson et al., 1994; Bellinger et al., 1995; Heyser et al., 1997) (for reviews, *see* Campbell and Chiang, 1996; Campbell, 1996; Mocke et al., 1996). At the histopathological level, the GFAP-IL6 mice show significant neurodegeneration, including loss and damage of neurons in the hippocampal formation and cerebellum (Campbell et al., 1993). Also, vascular changes such as blood–brain barrier breakdown (Brett et al., 1996) and angiogenesis (Campbell et al., 1993) occur in the CNS of GFAP-IL6 mice, both conditions being particularly pronounced in the cerebellum.

Several studies have identified neurophysiological abnormalities in the GFAP-IL6 transgenic mice (Gadient and Otten, 1994b; Steffenson et al., 1994; Bellinger et al., 1995; Heyser et al., 1997). GFAP-IL6 mice exhibit altered electroencephalographic (EEG) activity compared to normal mice, characterized by the presence of paroxysmal discharges and suppressed theta rhythm (Steffensen et al., 1994). In addition, recurrent inhibition, as determined by in vivo field potential recordings in conjunction with a paired-pulse stimulation protocol, is increased in the dentate gyrus of these mice. The disruption of theta rhythm and the presence of paroxysmal discharges could result from the loss of cholinergic inputs to the hippocampus (Steffensen et al., 1994; Buzsaki et al., 1989; Lahtinen et al., 1993). Consistent with this possibility, conditioning of the septohippocampal cholinergic input to the dentate gyrus of GFAP-IL6 mice fails to produce disinhibition in this brain region, in contrast to normal mice, and infusion of cholinergic agonists into the dentate restores the disinhibition in GFAP-IL6 mice (Steffensen et al., 1994). Thus, the disturbances in the EEG activity of GFAP-IL6 mice can be attributed to a functional denervation of the cholinergic input from the medial septum to the hippocampus (Steffensen et al., 1994). In support of this interpretation, dentate gyrus paired-pulse inhibition and facilitation are normal when studied in hippocampal slices isolated from GFAP-IL6 mice, indicating that the alterations in hippocampal function observed in vivo were caused by disruption of afferent inputs to the dentate gyrus (Vandenabeele and Fiers, 1991). However, long-term potentiation (LTP) was significantly reduced in the dentate gyrus of hippocampal slices obtained from GFAP-IL6 mice and studied in vitro (Vandenabeele and Fiers, 1991). LTP is a cellular model for learning and memory that is known to involve the NMDA receptor in the dentate gyrus (Burgard et al., 1989). IL-6 has been shown to influence NMDA receptor-mediated function and neurotoxicity. Thus, a potential pathway exists for the disruption of NMDA receptor-mediated memory formation by chronic exposure to IL-6. Behavioral testing has confirmed that GFAP-IL6 mice have significant deficits in learning (Heyser et al., 1997). These mice show a progressive decline in avoidance learning that closely corresponds to the level of neuropathology (Heyser et al., 1997).

In addition to cognitive deficits, the GFAP-IL6-transgenic mice exhibit a number of motor problems, such as motor incoordination, ataxia, and tremor (Campbell et al., 1993). These deficits are suggestive of cerebellar dysfunction, and appear to correspond with the severe neuropathology observed in the cerebellar cortex of these mice (Campbell et al., 1993). Using the GFAP-IL6-transgenic mice, we have recently investigated the effects of chronic IL-6 exposure on the physiology of cerebellar Purkinje neurons (Nelson et al., 1997), the sole output neuron of the cerebellar cortex and a crucial element in the integrative properties of the cerebellum. We found that Purkinje neurons in cerebellar slices from transgenic mice have a reduced spontaneous firing rate, as well as a higher incidence of oscillatory firing patterns. In addition, the response of Purkinje neurons to excitatory synaptic input from climbing fibers was altered in GFAP-IL6 mice. The response to climbing-fiber stimulation is characterized by an excita-

tory response known as a complex spike, which is often followed by a brief suppression of spontaneous firing, termed a climbing-fiber pause. Although there were no detectable changes in the appearance of complex spikes in GFAP-IL6 mice, the pause in spontaneous-firing activity following complex spikes was significantly longer in Purkinje neurons from GFAP-IL6 mice compared to control mice. Such alterations in Purkinje-neuron physiology caused by chronically elevated IL-6 could result in pronounced changes in cerebellar function.

In these studies of the cerebellum and hippocampus, it was not possible to determine whether the deficits in function in the GFAP-IL6 mice were because of direct effects of IL-6 on neuronal physiology or because of indirect effects of IL-6 such as the induction of neuropathology or alterations of CNS development. Regardless, it is obvious that chronic exposure to elevated levels of IL-6 can lead to severe impairments of normal CNS function.

IL-6 in CNS Disease

Several lines of evidence from both experimental studies in animals and clinical studies in humans indicate that elevated expression of IL-6 in the CNS occurs in CNS injury, infection, inflammation, and other disorders. However, in most cases, IL-6's role in pathologic processes remains to be defined. In general, IL-6 is only one of several cytokines that are elevated in CNS disease, injury, or inflammation, suggesting that cytokines work in concert in the CNS, as occurs in the periphery, to either produce CNS damage or repair injured tissue. Various conditions that induce IL-6 production in the CNS parenchyma or CSF are summarized in Table 2 (*see* also reviews Ershler et al., 1994; Merrill, 1992; Navikas and Link, 1996). The majority of information currently available on IL-6 levels in CNS disease comes from measurement of IL-6 levels in the CSF, a CNS region that is accessible with only minor injury to the animal or patient.

High levels of IL-6 in the CSF are found in patients with CNS infections including bacterial and viral meningitis, viral infections, encephalitis, and HIV infection (Eddleston and Mucke, 1993; Perrella et al., 1992a; Gallo et al., 1989; Achim et al., 1993; Gallo et al., 1991 Matsuzono et al., 1995; Waage et al., 1989; Houssiau et al., 1988; Heyes et al., 1995; Perrella et al., 1992b; Helfgott et al., 1989). The source of IL-6 appears to be CNS cells in some of these conditions, since elevated levels of IL-6 in the CSF occurs before leukocytes migrate to the CNS from the circulation, and CSF levels of IL-6 are higher than serum levels (Eddleston and Mucke, 1993; Matsuzono et al., 1995; Waage et al., 1989; Helfgott et al., 1989). In the HIV-infected brain, activated microglia (the CNS-cell type susceptible to HIV infection) and infiltrating blood cells (infected and uninfected with HIV) are considered to be a primary source of IL-6. Astrocytic production of IL-6 may contribute as well. In the monkey model of HIV infection (simian immunodeficiency virus; SIV), microglia derived from the monkey CNS and studied in culture after infection with SIV either in vivo or in culture, produced high levels of IL-6 (Sopper et al., 1996). LPS stimulation of the microglia enhanced IL-6 production. Moreover, IL-6 production by the cultured microglia was greater than that observed in cultured peripheral blood macrophages treated in a similar manner (Sopper et al., 1996). Blood monocytes/macrophages isolated from humans have been shown to produce high levels of IL-6 (e.g., 3 ng/mL) when infected by HIV in vitro (Nakajima et al., 1989). Elevated levels of IL-6 in the CSF during bacterial or viral infection of the CNS have also been demonstrated in animal studies (Frei et al., 1989; Houssiau et al., 1988; Frei et al., 1988; Rubio and Sierra, 1993; Rodriguez et al., 1994; Gijbels et al., 1990).

CNS injury also results in elevated levels of IL-6 in the CNS. CSF levels of IL-6 are increased in subarachnoid hemorrhage (Mathieson et al., 1993), experimental ischemia (Saito et al., 1996; Maeda et al., 1994; Wang et al., 1995), and in stroke patients (Tarkowski et al., 1995). For example, in transient-global ischemia in the gerbil, IL-6 levels are increased in several brain regions during the early recirculation period (<6 h) following a 10-min ischemic insult

(carotid-artery occlusion) (Saito et al., 1996). The elevation in IL-6 levels occurs with a delay (approx 3 h) and is maintained for up to 96 h. TNF-α and IL-1β levels are also increased during this period and may induce the expression of IL-6. Infiltrating blood cells are unlikely to be the source of cytokines in these studies since they are not detected in the CNS during the early phase of recirculation (<24 h; Jander et al., 1995). Increased IL-6 mRNA levels are also observed in experimental ischemia, with significant increases detected by 3 h following the ischemic insult (Wang et al., 1995).

Elevated levels of IL-6 in the CSF and brain parenchyma were reported for patients with traumatic brain injury, with the highest increases occurring in the early days after trauma (Kossman et al., 1995, 1996). Consistent with these observations, experiments in animal models showed an increase in CNS levels of IL-6 in traumatic brain injury (Taupin et al., 1993). Infiltrating macrophages and neutrophils and resident CNS microglia were evident at the site of the lesion in one animal study, suggesting that these cell types contribute to the increased IL-6 levels (Woodroofe et al., 1991). Traumatic injury to astrocytes in culture induces an increase in IL-6 production (Hariri et al., 1994), implicating a role for astrocytes in the increased levels of IL-6 in brain injury.

In patients with brain tumors, IL-6 levels (measured by bioassay) in the CSF range from 10–1600 U/mL, considerably higher than that present in the sera of these patients or in the CSF of control patients (<40 U/mL) (Leppert et al., 1989). The CSF levels of IL-6 did not correlate with the type of tumor (e.g., glioblastoma, astrocytoma, oligodendroglioma). Increased IL-6 levels were also observed in pituitary tumors (Tsagarakis et al., 1992).

Other CNS diseases in which IL-6 has been implicated include systemic lupus erythematosus (Yeh et al., 1994; Hirohata and Miyamoto, 1990), Parkinson's disease (Moji et al., 1994), multiple sclerosis (Merrill, 1992; Yamada et al., 1995), sudden infant death syndrome (Vege et al., 1995), and Alzheimer's disease. For example, IL-6 immunoreactivity is found in amyloid plaques in the CNS of patients with Alzheimer's disease but not in plaques in the CNS from control patients without dementia (Kossmann et al., 1995; Bauer et al., Strauss et al., 1992; Hull et al., 1996; Huell et al., 1995). Biochemical measurements also indicate an elevated level of IL-6 in the CNS of Alzheimer's patients (Wood et al., 1993). However, CSF levels of IL-6 were not elevated in patients with Alzheimer's dementia (Yamada et al., 1995) (*see also* reviews Berkenbosh et al., 1992; Hull et al., 1996; Dickson et al., 1991).

Taken together, these studies of CNS diseases indicate a prominent role for IL-6 in CNS pathology. However, like other actions of IL-6 outlined above, considerably more work needs to be done in terms of identifying the role of IL-6 in different disease states, resolving the cellular and molecular mechanisms mediating IL-6's CNS actions, and in clarifying the relationship between IL-6's physiological and pathological roles.

Future Directions

The relatively recent discovery that IL-6 and other cytokines commonly considered to be "immune-cell factors" are expressed by resident cells of the CNS is of considerable interest and has opened new areas of scientific investigation that are still in their infancy. Numerous questions are waiting to be addressed, several of which are noted below, or perhaps even defined. It is unlikely that a complete understanding of normal CNS function or dysfunction in the diseased state will be achieved without a detailed knowledge of the physiological and pathological actions of IL-6 and other immune-cell factors in the CNS. Information from numerous disciplines will undoubtedly be required, including studies utilizing behavioral, anatomical, biochemical, physiological, and molecular biological approaches.

The localization of IL-6 mRNA and IL-6R mRNAs to some CNS neuronal types has raised the interesting possibility that IL-6 may play a role as a signaling molecule (i.e., a neurotransmitter or neuromodulator) that commu-

nicates information between neurons of the CNS. This communication process, referred to as synaptic transmission, is the primary mechanism by which the CNS accomplishes its tasks. Synaptic transmission typically occurs between neurons of defined pathways and is achieved by release of a chemical signal (i.e., a neurotransmitter) from one neuron and detection of the chemical signal by a second neuron at sites of synaptic contact between the neurons. If IL-6 plays a role in this communication process, one would expect that features that are characteristic of synaptic transmission would also be exhibited by an IL-6 pathway. For example, one would expect that IL-6 and its receptor would be present at synaptic sites, that IL-6 release would be induced by neuronal activity in a calcium-dependent manner that is characteristic of neurotransmitter release, and that IL-6 would alter the physiological properties of the neuron receiving the chemical signal. To date little or no attention has been paid to this potentially important role of IL-6, and future studies addressing this issue are clearly needed.

IL-6 could also mediate bidirectional signaling between neurons and glial cells. In this case, sites of IL-6 release and IL-6Rs may be widely distributed on the cellular surfaces. However, issues such as conditions inducing IL-6 release, the cellular sites of release, the mechanisms of release, and the physiological actions of IL-6 on the target cells are still of critical importance for an understanding of such a communication pathway. As outlined above, astrocytes have been shown to synthesize and secrete IL-6 in vitro when stimulated by physiological (e.g., neurotransmitters) or pathological signals. Astrocytes are closely associated with neurons and ideally situated to communicate information to neurons or receive information from neurons or other cell types, for example microglia. A communication system involving these three cell types (neurons, astrocytes, and microglia) is an exciting possibility. Such a system could have significant impact on CNS function, especially under conditions of inflammation and injury when cytokine levels are elevated in the CNS. Future studies are needed to further explore this possibility.

Studies to date indicate that IL-6 levels are low in the CNS under normal physiological conditions but are elevated in several disease states. This observation raises the interesting possibility of dose-dependent pathological actions of IL-6 in the CNS. Relatively little is known about the effects of physiological or pathophysiological concentrations of IL-6 on the function of CNS cells. Thus, studies on this topic will be of particular interest. Whereas of these studies will involve the use of in vitro systems, studies in vivo will eventually be required. In vitro preparations of CNS cells are generally derived from embryonic tissue and the properties of embryonic cells may differ from the properties expressed by mature CNS cells in vivo.

The IL-6 receptor differs structurally and functionally from other receptors, such as neurotransmitter receptors, that are often a focus of studies on CNS function and dysfunction. Neuro-transmitter receptors typically transduce signals that have direct and relatively immediate influences on neuronal activity. In contrast, the IL-6 transduction pathway appears to be linked to processes involving gene transcription. However, the majority of information on the IL-6 transduction pathway and subcellular targets of pathway activation comes from studies of peripheral cells. CNS cells differ structurally and functionally from peripheral cell types and it is likely that the consequence of IL-6 receptor activation will also differ. Thus, detailed studies of the transduction pathway and subcellular targets of IL-6 actions in CNS cells are clearly needed.

In addition to information at the cellular and subcellular level, it will be important to characterize the regional distribution of IL-6 and IL-6R in the CNS. The CNS is a highly organized structure with various brain regions and neuronal pathways subserving different functions. Thus, identifying the regional distribution of IL-6 and IL-6R will be an important step toward an understanding of the role(s) of IL-6 in the CNS.

In summary, whereas much is known about IL-6 actions in the CNS, the surface has been barely scratched, and many interesting and important areas of research are waiting for eager scientific investigation. Hopefully, many will take up the challenge.

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