Interleukin-6 and Its Receptor: A Paradigm for Cytokines

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Many cytokines and cytokine receptors involved in the regulation of hematopoiesis, immune responses, and inflammation have been identified and characterized at the molecular level. Several characteristic features of cytokines, such as pleiotropy and redundancy, are now more clearly understood on the basis of their molecular structures. Accumulating evidence has demonstrated an intimate link between cytokines and various diseases such as allergy, autoimmune diseases, and cancer. The pathogenesis of these diseases and therapies to treat them will be discussed based on insights derived from cytokine research.

Communication between cells is essential for a wide variety of biological functions. One way cells interact in immune, hemopoietic, and neuronal systems is through soluble mediators called cytokines or interleukins. These molecules exert their biological effects through specific receptors expressed on the surface of target cells. Many cytokines and their receptors have been identified and characterized at the molecular level. These studies have observed that most cytokines function pleiotropically; exhibiting a wide range of biological effects on cells. Moreover, cytokines function in a redundant manner; different cytokines can act on the same cell type to mediate similar effects. Receptor studies have shown that many cytokine receptors consist of two polypeptide chains, a ligand-binding receptor, and a nonbinding signal transducer. This arrangement may explain the redundant effects of cytokines because different ligand-binding molecules can share the same signal transducer.

This review focuses on interleukin-6 (IL-6) its receptor (IL-6R), and on the signal transduction mechanism of IL-6 as a model system in which to study cytokine action. The roles of IL-6 in inflammation, viral infection, autoimmunity, and cancer will also be presented because emerging evidence demonstrates an intimate link between cytokines and several diseases.

IL-6, a Multifunctional Cytokine

Since the discovery of T cell–B cell interaction in the antibody response, the characterization of molecules that mediate the helper function of T cells has been a central issue in immunology. In the early 1970s, culture supernatants of T cells were demonstrated to contain an activity that induces immunoglobulin secretion in B cells (*1*). A few years later, two soluble mediators involved in immune regulation were functionally defined: IL-1 as a macrophage-derived mitogenic factor and IL-2 as a T cell–derived helper factor. At that time, IL-2 was believed to regulate immunoglobulin production. Since then, factors regulating B cell growth and differentiation have been studied extensively. At least three factors distinct from the initially characterized cytokines, IL-1 and IL-2, have been identified (*2*). In 1986, these molecules were cloned and designated IL-4, IL-5, and IL-6 (*3*). Subsequent studies with recombinant molecules and antibodies revealed that these interleukins function not only in B cells but also display a wide variety of biological effects in other tissues and cells. IL-6 exemplifies this diversity of function (Table 1) in that (i) it acts as a hepatocyte-stimulating factor and induces various acute-phase proteins in liver cells; (ii) it acts on hematopoietic stem cells in cooperation with IL-3 to promote the transition from the G_0 to the G_1 phase of the cell cycle; (iii) it induces maturation of megakaryocytes, resulting in an increase in platelets; (iv) it acts as a potent growth factor for human myeloma and murine plasmacytoma cells; (v) it induces differentiation of M1 murine myeloid leukemic cells into macrophages, as does leukemia inhibitory factor (LIF); and (vi) it induces neuronal differentiation of PC12 pheochromocytoma cells in a manner similar to that induced by nerve growth factor (NGF) (*4*).

Cytokine Receptor Family

Cloning of the cDNAs encoding the cytokine receptors was initially difficult because these proteins are expressed in low amounts; however, this problem was overcome by the development of expression cloning methods. In 1988, the cDNAs encoding the IL-1 and IL-6 receptors were cloned (*5*, *6*). Subsequent characterization revealed that the entire extracellular portion of the IL-1 receptor consists of three immunoglobulin-like domains, a signature of the immunoglobulin superfamily. This family includes many other growth factor receptors. The IL-6 receptor has a single immunoglobulin-like domain in the NH_2-terminal end of the extracellular region. Deletion of this domain does not affect ligand-binding activity; the remainder of the extracellular region, however, is essential for ligand binding. From 1989 to 1991 additional cytokine receptors were cloned, including IL-2R(β), IL-3R, IL-4R, IL-5R, IL-7R, erythropoietin (EPO)-R, granulocyte colony-stimulating factor (G-CSF)-R, granulocyte-macrophage colony-stimulating factor (GM-CSF)-R, and LIF-R (*7–10*). These receptors share structural features in their extracellular domains that were initially found in the IL-6 receptor and constitute a new family of cytokine receptors (*11*).

The homologous region of this cytokine receptor family consists of about 200 amino acids and is characterized by four conserved cysteine residues in the NH_2-terminal half and a tryptophan-serine-(one amino acid)-tryptophan-serine (WSXWS) motif in the COOH-terminal half. This region contains two fibronectin type III modules, in tandem, each of which was predicted to be composed of seven folds of anti-parallel β strands (*11*, *12*). The similarity of these structural features in the conserved domain suggests that the members of the cytokine receptor family evolved from a common ancestral gene.

Interaction of a Receptor and a Signal Transducer

The intracytoplasmic portions of cytokine receptors do not include sequences known to be important in signal transduction, such as tyrosine kinase domains. Furthermore, the intracytoplasmic portions of IL-6R, IL-3R (human), IL-5R, and GM-CSF-R are very short (*6*, *8*). In IL-6R, this region can be deleted without affecting IL-6 signal transduction (*13*), suggesting that an associated molecule is responsible for mediating the IL-6 signal.

Such an associated molecule was found to be required for signal transduction in the IL-6R system (*13*, *14*). Thus, the IL-6R

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system consists of the 80-kD IL-6R and a 130-kD signal transducer (gp130) that lacks IL-6–binding activity (Fig. 1). The binding of IL-6 to IL-6R triggers the association of the receptor and gp130. Whereas the expression of an IL-6R cDNA in an IL-6R–negative cell conferred only low-affinity binding sites, coexpression of the cDNAs for IL-6R and gp130 formed both low- and high-affinity binding sites. This result shows that gp130 participates in the formation of high-affinity binding sites despite the lack of IL-6–binding capability.

The functional redundancy of cytokines can now be explained by the interactions between multiple receptors and a common signal transducer. The gp130 protein serves as a signal transducer for IL-6, LIF, oncostatin M (OSM), and ciliary neurotrophic factor (CNTF). LIF was originally identified as a cytokine that both inhibited growth of M1 cells and induced their differentiation into macrophages (*15*). Later, LIF was shown to be a multifunctional cytokine whose activities overlapped with those of IL-6, including the effect on M1 cells (*16*). A cDNA encoding the LIF receptor (LIF-R) was cloned and the expression of this cDNA in COS cells was shown to generate specific low-affinity binding sites for LIF (*10*). Moreover, as with IL-6, LIF-responding cells express both high- and low-affinity LIF binding sites, suggesting that another high-affinity converting subunit of LIF-R might be found. Subsequently, this converter was cloned and shown to be identical to the IL-6 signal transducer, gp130 (*17*).

OSM is a cytokine that was originally identified as a growth inhibitor of human melanoma cells. OSM is structurally similar to LIF and IL-6 and shares multiple functions with these two factors (*18*); thus, gp130 might also be involved in the signaling processes triggered by OSM. Although gp130 binds OSM with low intrinsic affinity, this binding affinity increases when gp130 is coexpressed with LIF-R. The latter molecule has no OSM-binding capability, indicating that gp130 and LIF-R associate to form an OSM receptor complex (*17, 19*). However, some melanoma cells express OSM binding sites with higher affinity than that conferred by gp130 and LIF-R, even though these cells do not express LIF-R. This observation suggests that an unidentified receptor component exists for OSM (*17, 20*; Fig. 1). An antibody to gp130 completely blocks the OSM-induced production of acute-phase proteins in hepatoma cells and OSM-mediated growth inhibition of melanoma cells, which confirms that gp130 is essential for transducing the signals of OSM, in addition to those of IL-6 and LIF (*19, 21*).

Ciliary neurotrophic factor, initially identified by its ability to support the survival of ciliary neurons, has pleiotropic functions within the nervous system (*22*). These functions include the enhancement of motor neuron survival, induction of cholinergic differentiation of sympathetic neurons, and induction of astrocytic differentiation. In some neurons, LIF—also known as cholinergic differentiation factor (CDF)—elicits responses similar to those elicited by CNTF (*23*). Recently, a cDNA-encoding CNTF-R was cloned (*24*). Although this receptor is expressed exclusively in the nervous system, it has an extracellular domain that is homologous to that of IL-6R. Furthermore, CNTF-R has no transmembrane domain but is instead anchored to the membrane by a glycosyl-phosphatidylinositol (GPI) linkage.

The absence of a cytoplasmic portion in the CNTF-R is similar to the observation that the IL-6R can transduce a signal even without its intracellular domain. These observations suggested that a separate signal transducer existed for the CNTF-R and that gp130 potentially was such a molecule. Recent studies with CNTF-responsive cell lines have confirmed this. CNTF stimulation of MAH neuronal cells inhibited their growth and induced tyrosine-specific phosphorylation of gp130 (*25*). A complex of IL-6 and soluble IL-6R acts on several neuronal cell lines as well as on primary cultured neurons to initiate cellular responses similar to those induced by CNTF (*25*). Conversely, soluble CNTF-R plus

Table 1. Overlapping and specific functions of cytokines that use gp130 as a signal transducer.

Function	IL-6	LIF	OSM	CNTF
Immunological reaction	Immunoglobulin production T cell proliferation Cytotoxic T cell differentiation			
Hematopoiesis	Macrophage differentiation of M1 cells Stimulation of bone marrow progenitor cells Platelet production Proliferation of myeloma and plasmacytoma cells	Macrophage differentiation of M1 cells Stimulation of bone marrow progenitor cells Platelet production	Macrophage differentiation of M1 cells	
Inflammatory response	Acute-phase protein synthesis	Acute-phase protein synthesis	Acute-phase protein synthesis	
Neural development	Neurite outgrowth of PC12 cells Secretion of pituitary hormones Survival of postnatal forebrain neurons	Survival and generation of sensory neurons Survival of motor neurons Switch from adrenergic to cholinergic phenotype		Survival of ciliary neurons Survival of sympathetic, sensory, and motor neurons Switch from adrenergic to cholinergic phenotype Differentiation of type-2 astrocytes
Others	Proliferation of AIDS-KS cells, keratinocytes, renal mesangial cells, smooth muscle cells, and myoblasts Regulation of bone metabolism Inhibition of melanoma and breast carcinoma cell growth	Maintenance of embryonic stem cells Proliferation of myoblasts Regulation of bone metabolism Inhibition of lipoprotein lipase in adipocytes	Maintenance of embryonic stem cells Proliferation of AIDS-KS cells and fibroblasts Inhibition of melanoma, breast, and lung carcinoma cells	

CNTF induced a human erythroleukemia cell line (TF1) that does not express the CNTF-R to initiate DNA synthesis (*21*). The proliferation of TF1 cells induced by soluble CNTF-R and CNTF was completely blocked by antibodies to gp130, indicating that gp130 was involved in the CNTF-signaling process. The CNTF stimulation induced tyrosine-specific phosphorylation of gp130 as well as that of a 190-kD protein, which is most likely LIF-R. This result suggested that LIF-R may also be part of the CNTF-R complex (*21, 25*).

Although these four cytokines have overlapping functions, each factor possesses its own specific activities (Table 1). Thus, whereas ubiquitously expressed gp130 is involved in the signal transduction of all four of these cytokines, the ability of gp130 to respond to each of these factors appears to be regulated by the expression of their specific receptor chains.

The formation of high-affinity sites as a result of the interaction of multiple different proteins was originally observed in the IL-2R system (*7, 26*), in which both the α and β chains possess a specific binding affinity for IL-2. In several cytokine receptor systems, such as those of IL-3, IL-5, GM-CSF, and NGF, the expression of the cloned receptor cDNAs conferred only low-affinity binding on the cell, although both low- and high-affinity binding are observed in cells responding to these cytokines (*8, 27*). This suggested the existence of other receptor systems similar to those of IL-6R or IL-2R. The human KH97 protein, which is highly similar to the mouse IL-3R, has been shown to be associated with IL-3R, IL-5R, and GM-CSF-R and is able to increase their respective binding affinities (*8, 28*). In addition, the generation of high-affinity NGF binding sites has been shown to involve *trk* proto-oncogene products (*29*).

Signal Transduction from gp130 to the Transcription Factor NF-IL6

As noted previously, most cytokine receptors and their signal transducers do not contain any of the signal transduction sequence motifs, such as the tyrosine kinase domains, that are observed in other growth factor receptors. Stimulation of target cells with cytokines does not usually generate biochemical changes, such as phosphatidylinositol (PI)-turnover or increases in intracytoplasmic Ca^{++}, suggesting that phospholipase C (PLC)-γ, which has been shown to interact with several growth factor receptors with tyrosine kinase domains, is not activated by cytokines. However, several cytokines, such as IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, G-CSF, GM-CSF, LIF, EPO, and CNTF have been shown to activate intracellular tyrosine kinases and induce the tyrosine-specific phosphorylation of cellular proteins (*30, 31*).

In the 277–amino acid cytoplasmic domain of gp130, a region consisting of ~60 amino acids proximal to the transmembrane domain was shown to be essential for signal transduction (*31*). Two short stretches of amino acids from this region are highly conserved among many cytokine receptors and signal transducers belonging to the cytokine receptor family. Thus, a common or structurally related signaling molecule (or molecules), such as an intracytoplasmic tyrosine kinase, may interact with this region of similarity. In the IL-6 signaling pathway, the stimulation of target cells with a complex of soluble IL-6R and IL-6 induces the homodimerization of gp130 and the tyrosine-specific phosphorylation of gp130 (*32*). At present, it remains unclear which tyrosine kinase (or kinases) interacts with gp130 and which downstream signaling molecules are the targets for this tyrosine kinase. The IL-2Rβ chain was shown to interact with the tyrosine kinase Lck (*33*). It is unknown whether the IL-2Rβ chain itself is a substrate of Lck or whether Lck, linked to the receptor, activates other metabolic processes.

Signals provided through membrane receptors can affect the functions of cells mainly through the modulation of the activity of sequence-specific transcription factors. In the IL-6 signaling pathway, the activation of acute-phase genes in hepatocytes provides a suitable model system for studying this complex signal transduction cascade. NF-IL6 was originally identified as a transcription factor involved in the induction of IL-6 expression by IL-1 (*34*). The cDNA encoding NF-IL6 was cloned (*35*), and the deduced amino acid sequence revealed a high degree of similarity to a liver-specific transcription factor, C/EBP, the first nuclear factor proposed to contain a leucine zipper structure (*36*). Subsequent studies revealed that NF-IL6 could bind to the IL-6 responsive element in the promoters of acute-phase genes and that NF-IL6 was involved in the regulation of acute-phase gene expression in hepatocytes (*37*). Thus, NF-IL6 is a transcription factor that regulates the expression of the IL-6 gene and other IL-6 inducible genes.

The posttranslational modification of NF-IL6 is necessary for DNA-binding activity and transactivating capacity. In response to IL-6, NF-IL6 is phosphorylated at specific serine residues, indicating that a serine kinase in nuclei is activated by IL-6 stimulation (*38*). At present, little is known about the signaling cascade from the tyrosine kinases to the serine kinases. Recently, several lines of evidence have implicated Ras in the transduction of signals generated by IL-2, IL-3, IL-6, GM-CSF, and macrophage (M)-CSF (*39*). Although the pathways that transmit signals from cytokine receptors to the genes responsible for cellular proliferation, growth inhibition, and differentiation are still unknown, studies to identify kinases or molecules associated with cytokine receptors or transcription factors should improve our understanding of this area.

Role of IL-6 in Inflammation, Viral Infection, and Autoimmunity

The first example of a disease associated with abnormal IL-6 production was cardiac myxoma, a benign heart tumor (*40*). Patients with cardiac myxoma produce multiple types of autoantibodies and display autoimmune symptoms. Cardiac myxoma cells express IL-6 mRNA and protein, and

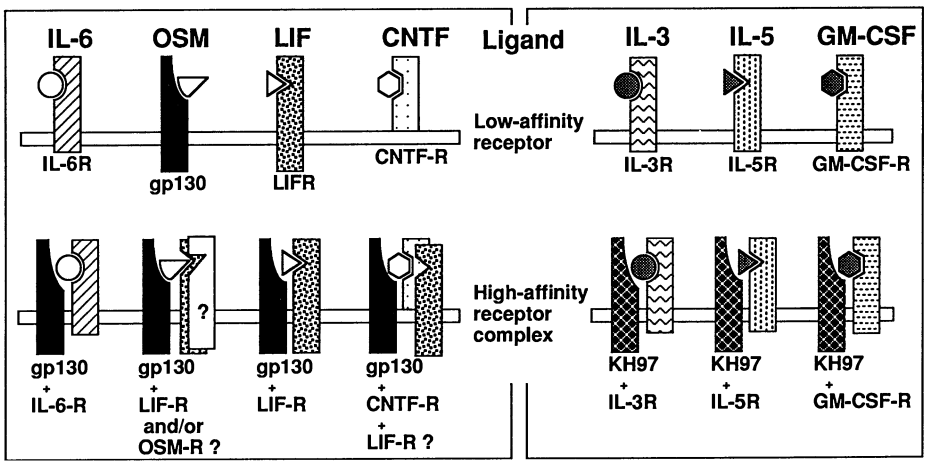

Fig. 1. Schematic models of the multisubunit receptors for IL-6, OSM, LIF, and CNTF (left) and IL-3, IL-5, and GM-CSF (right). In the IL-6R complex, IL-6 triggers the association of a low-affinity ligand-binding subunit (IL-6R) and a nonbinding signal transducer (gp130) to form a high-affinity complex. The existence of common affinity converters responsible for signaling (gp130, left; KH97, right) would explain the overlapping functions of these cytokines.

patients with this disease display elevated serum levels of IL-6. After surgical removal of myxomas, the serum concentration of IL-6 decreases to normal amounts, and a regression of the immunologic response occurs (*41*). This experiment suggests to us that abnormal constitutive production of IL-6 may be involved in the development of an autoimmune state. Elevated quantities of IL-6 are detected in the synovial fluids from affected joints and in sera of patients with active rheumatoid arthritis (RA) (*42*). Serum levels of IL-6 correlate well with the disease activity of RA. In addition to IL-6, several other cytokines, such as IL-1, IL-8, and tumor necrosis factor (TNF), are present in increased amounts in patients with RA (*43*). Coordinated production of IL-6 and IL-8 is often observed in various other inflammatory conditions. The promoters of the *IL-6* and *IL-8* genes contain binding sites for NF-IL6 and NF-κB; both of these sites are essential for expression of these genes (*44*). The promoter regions of the *IL-1* and *TNF* genes contain NF-IL6 binding sites (*45*). Thus, a common signal (or signals) that activates NF-IL6 or NF-κB, or both, may simultaneously induce the expression of several inflammatory cytokines, including IL-6.

These transcription factors may be activated or modulated by viral infection. Viral infections have long been implicated in the pathogenesis of some autoimmune diseases. Human T cell leukemia virus (HTLV)–1 infection induces constitutive IL-6 production in T cells, even though normal T cells do not express IL-6. Transgenic mice expressing the HTLV-1 pX protein develop a type of arthritis resembling rheumatoid arthritis (*46*) and show increased expression of various inflammatory cytokines, including IL-6 and IL-1. These results strongly suggest that the pX protein might activate a cellular transcription factor such as NF-IL6 or NF-κB, or factors, responsible for the expression of inflammatory cytokines.

Another example of the association between viral infection and abnormal IL-6 production is HIV infection. HIV-infected AIDS patients show high serum concentrations of IL-6 (*47*). HIV-Tat protein has a growth-promoting activity in AIDS–Kaposi's sarcoma (KS) cells (*48*). Transgenic mice containing the *tat* gene under the control of the HIV-LTR develop a KS-like disease (*49*). The Tat-induced growth of KS cells can be specifically inhibited by antisense IL-6 oligonucleotides, suggesting that Tat induces KS cell proliferation, at least in part, through an IL-6–dependent autocrine mechanism (*50*). Studies should determine whether HIV-Tat activates the IL-6 promoter through the activation of NF-IL6 or NF-κB, or both. Recently, OSM was found to be a potent mitogen for AIDS-KS cells (*51*). After exposure to OSM, AIDS-KS cells assume a spindle morphology and have an increased ability to proliferate in soft agar. Because both IL-6R and OSM-R use gp130 as a signal transducer, these results indicate that gp130 is involved in the growth signaling pathway in AIDS-KS cells. Thus, blocking the gp130 signaling pathway may be of therapeutic value in treating AIDS-KS.

Role of IL-6 in Myelomas and Plasmacytomas

Recombinant IL-6 acts as a potent growth stimulator in human myeloma and murine plasmacytoma cells, suggesting that it may be involved in the pathogenesis of multiple myelomas (*52, 53*). Studies on human myeloma cells freshly isolated from the bone marrow of patients demonstrate that IL-6 is an autocrine growth factor in human myelomas (*53*). Several other cytokines, such as IL-1 and TNF, are also secreted from myeloma cells and are responsible for the induction of IL-6 in the stromal cells of bone marrow (*54*). Therefore, IL-6 autocrine as well as paracrine mechanisms operate in the generation of human multiple myelomas. Administration of a murine monoclonal antibody against human IL-6 to myeloma patients was effective in inhibiting the growth in vivo of myeloma cells, thus confirming the role of IL-6 in the growth of myeloma cells (*55*).

Studies in transgenic mice, in which the human IL-6 gene was expressed under the control of immunoglobulin μ-chain enhancer (Eμ-IL-6) confirm that the constitutive production of IL-6 in B cells can lead to the generation of plasmacytomas (*56*). In the mouse B6 strain, however, expression of the Eμ-IL-6 transgene results in massive plasmacytosis but no monoclonal plasmacytomas. Introduction of the Eμ-IL-6 transgene into BALB/c mice results in the generation of monoclonal and transplantable plasmacytomas (*57*). Furthermore, these plasmacytomas were found to carry a (12;15) chromosomal translocation commonly observed in mineral oil–induced murine plasmacytomas. These results show that both the abnormal production of a tissue-specific growth factor (IL-6) and some genetic feature of BALB/c mice are necessary and sufficient for the generation of plasmacytomas. This finding may explain the mechanism of mineral oil–induced plasmacytoma generation in BALB/c mice, a phenomenon initially reported more than two decades ago (*58*). Intraperitoneal injection of mineral oil generates granulomas that produce large amounts of a plasmacytoma growth factor and leads to the development of plasmacytomas. Recently, this plasmacytoma growth factor has been characterized and shown to be identical to IL-6 (*52*).

Possible Clinical Applications of IL-6

Recombinant growth factors such as EPO and G-CSF are widely used for the treatment of anemia in patients with renal failure (EPO) and for neutropenia in cancer patients undergoing cytotoxic therapy (G-CSF) (*59*). Thrombocytopenia induced by the treatment of cancer patients with cytotoxic drugs or after bone marrow transplantation remains a major clinical problem and limits the application of these treatments. The identification of hematopoietic cytokines with thrombopoietic activity has been of major interest for the past decade. A dramatic increase in the number of mature, multinuclear megakaryocytes was observed in the bone marrow of IL-6 transgenic mice, suggesting a role for IL-6 in megakaryocyte maturation (*56*). In fact, IL-6 promotes maturation of murine megakaryocytes in vitro (*60*). In vivo administration of recombinant IL-6 in primates increases platelet counts by 100% (*61*). These observations could be of major practical importance, and further studies on various combinations of hematopoietic cytokines, IL-6, IL-3, and stem cell factor (c-kit ligand) may lead to new therapeutic approaches for thrombocytopenia.

IL-6 is multifunctional and produces both favorable and unfavorable effects on human health. Dysregulation of IL-6 expression is linked to the occurrence of cancer and autoimmune disease, thus, inhibitors of IL-6 may have potential therapeutic applications. Crystallographic studies on ligands, receptors, and signal transducers may provide information leading to the synthesis of inhibitors of cytokines. Molecular studies on the transcription factors involved in the regulation of cytokine genes may also provide information about compounds that could modulate transcription factor activity and thus alter the regulation of cytokine gene expression.

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Molecular Diversity of Glutamate Receptors and Implications for Brain Function

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The glutamate receptors mediate excitatory neurotransmission in the brain and are important in memory acquisition, learning, and some neurodegenerative disorders. This receptor family is classified in three groups: the *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)–kainate, and metabotropic receptors. Recent molecular studies have shown that many receptor subtypes exist in all three groups of the receptors and exhibit heterogeneity in function and expression patterns. This article reviews the molecular and functional diversity of the glutamate receptors and discusses their implications for integrative brain function.

Signal transmission at neuronal synapses is mediated by a variety of receptors that specify neurotransmitter interactions and transmit information into target cells. The vast majority of synapses in the central nervous system (CNS) uses glutamate as a neurotransmitter to produce rapid neuronal excitation (*1*). Glutamate neurotransmission also participates in neuronal plasticity and neurotoxicity. Neuronal plasticity elicited by glutamate is exemplified by long-term potentiation (LTP) in the hippocampus and long-term depression (LTD) in the cerebellum, which are long-lasting, use-dependent enhancement and depression in synaptic efficacy, respectively (*2*, *3*). Because memory is postulated to be encoded in the brain through long-lasting changes in synaptic efficacy produced by the prior use of synapses, LTP and LTD are believed to be fundamental processes that underlie information storage in the brain. Excess glutamate neurotransmission, on the contrary, triggers neuronal degeneration and neuronal cell death (*4*). For example, during brain ischemia and hypoglycemia, massive stimulation of glutamate receptors by high concentrations of extracellular glutamate causes deterioration of neuronal activity and finally leads to neuronal cell death. Gluta-

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