Correspondence

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A brief summary regarding the roles of interleukin-11 in neurological diseases

Marat Airapetov[1,2,*], Sergei Eresko[1,3], Polina Ignatova[1], Andrei Lebedev[1], Evgenii Bychkov[1], Petr Shabanov[1,4]

[1] Department of Neuropharmacology, Institute of Experimental Medicine, St. Petersburg, Russia;
[2] Department of Pharmacology, St. Petersburg State Pediatric Medical University, St. Petersburg, Russia;
[3] Research and Education Center for Molecular and Cellular Technologies, St. Petersburg State Chemical Pharmaceutical University, St. Petersburg, Russia;
[4] Department of Pharmacology, Kirov Military Medical Academy, St. Petersburg, Russia.

SUMMARY Interleukin 11 (IL-11) was discovered in 1990 in fibrocyte-like stromal cells of the bone marrow, but there has recently been an increased interest in the cytokine. Understanding the physiological roles of cytokines will allow their use as pharmacological agents in clinical practice. Studies have indicated that IL-11 affects the mechanism for the development of a number of pathologies of the nervous system. IL-11 plays a significant role in the central nervous system. The local expression of this cytokine by nerve cells has been observed. The current work summarizes the results of studies which found that the cytokine affects the mechanism of development of pathologies of the central nervous system. In the near future, this cytokine may be used clinically to fix the mechanisms that are involved in the development of pathological conditions of the nervous system.

Keywords IL-11, IL-6 family, gp130, brain, neuroinflammation, neurodegeneration

In 1990, a new cytokine named interleukin 11 (IL-11) was discovered in fibrocyte-like stromal cells of the bone marrow (*1*). More than 30 years have passed since the discovery of IL-11. Initially, a study indicated that IL-11 is important to the process of hematopoiesis, and especially for the maturation of megakaryocytes (*1*). A study by Mehler *et al*. posited that there are similarities in the regulation of the processes of hemalymphopoiesis and neurogenesis by means of cytokines (*2*). The study's results confirmed that there are indeed similarities between the mechanisms that regulate these processes.

Further studies have shown that IL-11 and its components of the receptor complex are widely localized among various parts of the central nervous system (CNS), which may indicate the involvement of IL-11 in cascades of reactions that regulate various physiological processes in the CNS (*3-11*). IL-11 is expressed in hippocampal neurons, stimulating the proliferation of progenitor cells, so the cytokine is involved in the process of neurogenesis (*2*). These initial studies were probably the reason for further examination of this cytokine's involvement.

The current work has summarized information about the roles that IL-11 can play in the development of pathological conditions of the nervous system. The results of such studies can help to discover new ways to treat these pathological conditions where this cytokine and signaling cascades of IL-11 are involved.

1. IL-11 and its intracellular signaling cascade of reactions

IL-11 is a protein with an approximate molecular weight of 19 kDa. The IL-11 precursor (pre-IL-11) consists of 199 amino acid residues. The pre-IL-11 gene, consisting of 5 exons and 4 introns, is located on the 19th human chromosome (*12-15*). There are data on expression of the IL-11 protein in many tissues in the body (*16*).

IL-11 and components of its receptor complex are expressed in the brain (*3-7,9-11*). The expression of IL-11 was noted in the olfactory bulb, amygdala, basal ganglia, thalamus, midbrain, bridge, medulla oblongata, hippocampus, cerebral cortex, and cerebellum (*8-11*). Localization of the key receptor component of the gp130 protein was also found in the brain of rats (immunoreactivity was observed in both glial and neuronal cells) (*9*). Electron microscopy revealed that both types of gp130 immunoreactivity are mainly associated with the cytoplasmic membrane and are not precisely localized in synaptic sites (*9*). The results of RNA-Seq analysis also revealed the presence of IL-

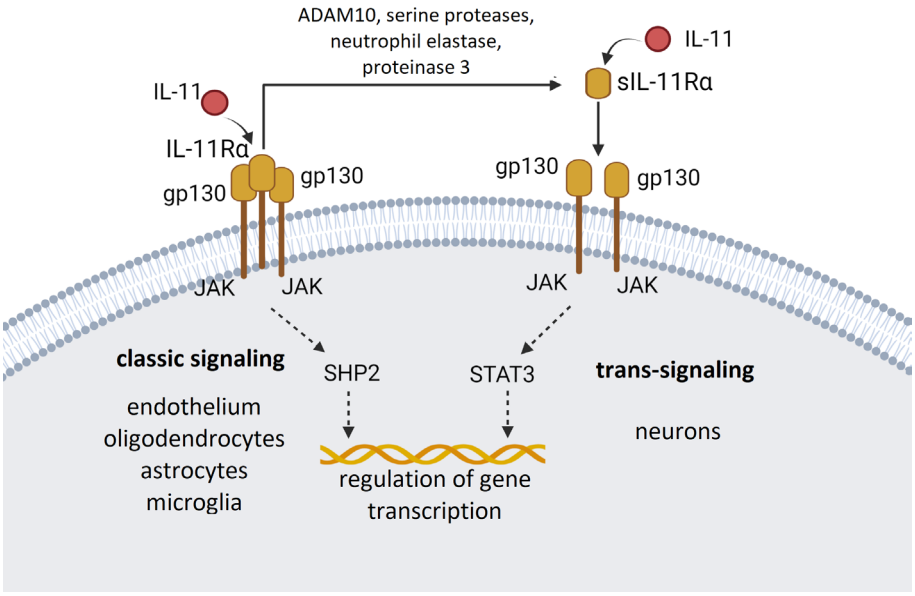

Figure 1. The interaction of IL-11 with the receptor complex serves as a signal to activate the JAK/SHP2–dependent pathway of intracellular signal transmission.

11, IL-11Ra, and gp130 mRNA among various brain structures. The level of IL-11 mRNA is insignificant in all types of cells of the nervous system, but IL-11Ra and gp130 mRNA is found in the greatest amount in astrocytes, microglia, and the endothelium (*10-11*).

Currently, there is no high-resolution structural data on the IL-11 signaling complex, although there is evidence that IL-11Ra and IL-6Ra are structurally similar (*17*). The interaction of IL-11 with the receptor complex serves as a signal to activate the JAK/SHP2 – dependent pathway of intracellular signal transmission (Figure 1). Another signaling pathway begins with phosphorylation of the STAT1 and STAT3 proteins (*12-15*). Unlike many cells that can serve as a source of cytokines such as IL-11, the expression of receptor subunits is more limited, which determines the more specific effect of cytokines on certain populations of cells in the body that can be directly activated by the IL-11 cytokine (*18*). In addition, part of the IL-11Ra receptor complex may not only be localized on the cell membrane but may exist in soluble form (*18*). Metalloprotease ADAM10, as well as serine proteases, neutrophil elastase, and proteinase 3 can cleave the ectodomain from IL-11Ra, and the ectodomain formed during cleavage serves as a soluble form of the receptor - sIL-11R (soluble IL-11R).

2. IL-11 affects the mechanism of development of neurological diseases

2.1. Alzheimer's disease

The ability of IL-11 to regulate the mechanism of pathologies in the nervous system was indicated in a neuroblastoma cell culture model of Alzheimer's disease (AD) (*16*). AD is characterized by the deposition of β-amyloid in the brain, and the increased production of β-amyloid peptide is considered to be one of the early events in the pathogenesis of AD. β-amyloid was found to activate L-phosphoserine phosphatase in neuronal cells (B104 rat neuroblastoma cells); that activation was inhibited by IL-11 while IL-11 inhibited neurotoxicity. The aforementioned study suggested that L-phosphoserine phosphatase may play a role in changing cellular metabolism in AD by increasing neurotoxicity and that IL-11 through its receptor system can act as a neuroprotector.

2.2. Multiple sclerosis

In 2006, researchers noted an increase in IL-11 in astrocytes and expression of IL-11R by oligodendrocytes in multiple sclerosis (*19*). Studies of astrocyte and oligodendrocyte cultures concluded that the IL-11/IL-11R pathway can play an important role in protecting oligodendrocytes in multiple sclerosis. When recombinant IL-11 was added to a culture of human fetal spinal cord cells, an increase in the number of oligodendrocytes was noted, an increase in the process of oligodendroglia branching was noted, apoptotic cell death decreased and IL-11 potentiated the formation of myelin. A 2009 study of knockout mice without the IL-11Ra gene (IL-11Ra$^{-/-}$ and IL-11Ra$^{+/-}$) revealed a pronounced neuroinflammatory process in spinal cord tissues, characterized by infiltration by macrophages, followed by demyelination and a decrease in the number of nerve cells (*5*). That study evaluated the effect of exogenous IL-11 on a culture of progenitor

oligodendrocytes of rats. The use of IL-11 increased cell survival by reducing the number of cells dying due to apoptosis and potentiating the process of cell division. In addition, exogenous IL-11 was able to reduce the activation of CD4 lymphocytes by inhibiting $CD11c^{++}$ cells, and IL-11 was able to regulate the production of effector cytokines by acting on $CD11c^{++}$ cells. A study of a cuprizone model of multiple sclerosis in mice found that overexpression of IL-11 caused by local delivery of a viral vector with the IL-11 gene to the lesion site reduced the degree of demyelination with simultaneous acceleration of the remyelination process (*6*). Microglia are known to participate in myelin phagocytosis, so that study's results may indicate that IL-11 is able to make adjustments to this process, but the mechanism by which microglia are involved in the effects caused by IL-11 remains to be determined. An in vitro experiment on the BV2 microglia cell line indicated that the addition of recombinant IL-11 in a dose-dependent manner reduced the degree of myelin phagocytosis (*6*). In addition, the experiment indicated that the use of IL-11 led to an increase in the thickness of the myelin layer; this indicates the ability of IL-11 to enhance the remyelination process, but the mechanism for this has yet to be studied. Studies have described the ability of IL-11 to inhibit the synthesis of TNFα, IL-1β, IL-12, and IL-6 and the production of NO by activated macrophages (*20,21*), but those studies did not report the level of pro-inflammatory mediators.

2.3. Autoimmune encephalomyelitis

In a model of autoimmune encephalomyelitis, mice were injected with 25 or 50 mcg/kg/day of recombinant IL-11 after the appearance of signs of encephalomyelitis (*5*). A dose of 50 mcg/kg/day led to a reduction in the severity of the disease: a decrease in the degree of demyelination, a decrease in the loss of oligodendrocytes, a decrease in inflammation, and a reduction in the number of CD3 lymphocytes. The use of lower doses was not reported to have a significant effect.

2.4. Ischemic stroke

In one study, the medial cerebral artery was occluded in mice in order to simulate ischemic brain damage (*7*). Results revealed a decrease in the expression of IL-11 protein and mRNA in the first 24 hours of ischemia. The administration of recombinant IL-11 showed the anti-inflammatory effects of the cytokine, which were characterized by a decrease in the markers of activation of astrocytes and microglia and a decrease in the mRNA of pro-inflammatory cytokines (IL1ß, IL-6, and TNFβ), but the level of mRNA of the anti-inflammatory cytokine TGFß1 increased, there was an increase in the level of superoxide dismutase, and a decrease in the level of malondialdehyde. This indicates a decrease in the level of oxidative stress in brain tissues.

2.5. Other research

Another finding warrants attention. A recent study found that cytokines of the IL-6 family can mediate an increase in the chemoresistance of medulloblastoma tumor cells. Conditioned in vitro with IL-6, OSM, LIF, or IL-11 cytokines, cultured medulloblastoma cells exhibit increased activity of JAK1/STAT3 signaling, while chemoresistance to a number of drugs begins to be noted (*22*). In addition, the use of gp130 inhibitors or JAK-canis inhibitors effectively overcame the resistance of medulloblastoma to vincristine in gp130-expressing cells. These findings may indicate the existence of restrictions on the use of recombinant IL-11 in a number of individual cases, but in vivo studies need to be conducted to clarify the observed phenomenon and to examine the indirect effect of IL-6 cytokines on other types of tumor cell lines.

Compliance with ethical standards: This article does not contain any research involving human or animal subjects.

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Conflict of Interest: The authors declare that they have no conflicts of interest.

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**Address correspondence to:*
Marat Airapetov, Department of Neuropharmacology, Institute of Experimental Medicine, 12 Academician Pavlova Street, St. Petersburg, 197376, Russia.
E-mail: interleukin1b@gmail.com

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