Neuroscience and Biobehavioral Reviews 37 (2013) 184–192

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

# Brain interleukin-15 in neuroinflammation and behavior

Weihong Pan[a,*], Xiaojun Wu[a,1], Yi He[a,2], Hung Hsuchou[a], Eagle Yi-Kung Huang[b], Pramod K. Mishra[a], Abba J. Kastin[a]

[a] Blood-Brain Barrier Group, Pennington Biomedical Research Center, Baton Rouge, LA 70808, USA
[b] Dept. of Pharmacology, National Defense Medical Center, Taipei, Taiwan

ARTICLE INFO

*Article history:*
Received 17 July 2012
Received in revised form
17 November 2012
Accepted 20 November 2012

*Keywords:*
Cytokine
Peptide
Interleukin-15
Depression
Anxiety
Memory
Neurobehavior
Neurotransmitter
Neurogenesis
Metabolic activity

ABSTRACT

Interleukin (IL)-15 is a ubiquitously expressed cytokine existing in both intracellular and secretory forms. Here we review the expression, regulation, and functions of IL15 and its receptors in the brain. IL15 receptors show robust upregulation after neuroinflammation, suggesting a major role of IL15 signaling in cerebral function. Involvement of the IL15 system in neuropsychiatric behavior is reflected by the effects of IL15, IL15Rα, and IL2Rγ deletions on neurobehavior and neurotransmitters, the effects of IL15 treatment on neuronal activity, and the potential role of IL15 in neuroplasticity/neurogenesis. The results show that IL15 modulates GABA and serotonin transmission. This may underlie deficits in mood (depressive-like behavior and decreased normal anxiety) and memory, as well as activity level, sleep, and thermoregulation. Although IL15 has only a low level of permeation across the blood–brain barrier, peripheral IL15 is able to activate multiple signaling pathways in neurons widely distributed in CNS regions. The effects of IL15 in "preventing" neuropsychiatric symptoms in normal mice implicate a potential therapeutic role of this polypeptide cytokine.



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## 1. Introduction

There is growing awareness of a role of cytokines in the structural and neurochemical basis of neuropsychiatric disorders. Cytokines are at the crossroads of inflammation and functional deficits in cognition and emotion. We review here the cerebral interleukin (IL)-15 system as a key player in the cytokine network that limits the consequences of neurochemical imbalance. IL15 receptors are robustly upregulated in mouse models of altered innate immunity and acquired immunity. Otherwise normal appearing IL15 receptor knockout mice show unusual cognitive deficits and mood disturbances. These exciting new findings prompted us to address the potential role of cerebral IL15 in mood and memory.

IL15 is a member of the 4 α-helix bundle family that was initially cloned in 1994 as a new T cell growth factor that competes with IL2 for receptor binding (Grabstein et al., 1994). In comparison with IL2 which has a relatively restricted expression in activated T cells, IL15 has a wider tissue and cellular distribution (Grabstein

* Corresponding author. Tel.: +1 225 763 2715; fax: +1 225 763 0265.
*E-mail address:* weihong.pan@pbrc.edu (W. Pan).
[1] Current address: Shanghai University of Traditional Chinese Medicine, Shanghai, China.
[2] Current address: Beijing Capitol University Department of Physiology, Beijing, China.

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http://dx.doi.org/10.1016/j.neubiorev.2012.11.009

et al., 1994; Bamford et al., 1996; Kitaya et al., 2000). IL15 acts through a trimeric receptor complex comprising IL15Rα, IL2Rβ, and IL2Rγ. The β and γ receptor subunits are shared by IL15 and IL2 and are essential in relaying signals for both cytokines (Waldmann et al., 1998; Waldmann and Tagaya, 1999). In many human and murine cell lines, IL15 shows high affinity binding, in contrast to IL2 that contains both high and low affinity binding sites (Giri et al., 1994). Like the multi-level control of IL15Rα and IL15 expression, the high affinity association between IL15Rα and IL15 suggests a highly efficient regulatory system.

A unique aspect of IL15 action is its juxtacrine and reverse signaling. With agonistic stimulation, membrane-bound IL15 phosphorylates mitogen-activated protein kinase (MAPK) and focal adhesion kinase (FAK) to increase cytokine secretion and cell adhesion and migration. IL15 can be trans-presented by its high-affinity receptor IL15Rα to adjacent cells that express IL2Rβ and IL2Rγ, without the necessity of IL15 binding to the heterotrimeric receptor complex (Schluns et al., 2005; Bulfone-Paus et al., 2006). Although most findings were observed in lymphocytes, it is possible that CNS parenchymal cells show a similar phenomenon. If proven, trans-presentation of IL15 could represent a novel path for neuron–glial interactions.

This review focuses on the cerebral IL15 system in normal and pathophysiological conditions. We first describe the distribution and known functions of IL15 and its receptors, some of which are shared with IL2. We then summarize the effects of IL15, IL15Rα, and IL2Rγ deletion on the neurobehavior of these knockout mice, as well as the effects of IL15 treatment on neuronal activity, including neurogenesis and synaptic plasticity. IL15 and its receptors have complex regulation at multiple levels, and significantly influence cerebral activity and animal behavior. This is illustrated by findings from measurement of neurotransmitter profiles in the knockout mice and assays of regulatory changes of IL15 receptors during neuroinflammation and autoimmune challenge.

## 2. Distribution and cellular functions of IL15 and its receptors in CNS regions, cell types, and subcellular organelles

IL15 and its receptors are expressed throughout the brain by either glial cells or neurons, and show developmental changes, regional differences, and regulation by inflammatory challenges (Hanisch et al., 1997; Kurowska et al., 2002; Wu et al., 2010c). In human fetal brain, mRNA for IL15 and IL15Rα is higher in the hippocampus and cerebellum than in the cortex and thalamus (Kurowska et al., 2002). During inflammation with disruption of the BBB, both immune cells and CNS parenchymal cells become sources of IL15.

In peripheral cells, IL15 is induced by interferon-γ, lipopolysaccharide (LPS), mycobacteria, and Toxoplasma gondii in macrophages and monocytes (Doherty et al., 1996). In the CNS, basal expression of IL15 is mainly seen in astrocytes and some projection neurons. In patients with multiple sclerosis (MS), there is increased intrathecal production of IL15 (Lee et al., 1996; Satoh et al., 1998; Kivisakk et al., 1998; Beck et al., 2005b). Within the CNS, IL15 affects nitric oxide production and growth of microglia (Waldmann and Tagaya, 1999). IL15 may play a protective role in host defense by increasing γδ-T cells, as shown by comparison studies in macrophages obtained from LPS-responsive C3H/HeN mice and LPS-hyporesponsive C3H/HeJ mice (Takano et al., 1998). IL15Rα might also confer neuroprotection, as IL15Rα knockout mice have five times more motor neuron death after facial nerve axotomy (Huang et al., 2007). IL15 induces sickness behavior; icv injection of IL15 dose-dependently increases non-rapid eye movement sleep and temperature, with the cost of an associated reduction of rapid eye movement sleep (Kubota et al., 2001).

IL15 can be proinflammatory to induce reactive gliosis. This is shown by reduction of the reactivity of both astrocytes and microglia by a blocking antibody against IL15 in the brain after LPS treatment (Gomez-Nicola et al., 2010). In cultured microglia, IL15 blockade reduces the activation of MAPK and nuclear factor (NF)-κB (Gomez-Nicola et al., 2008). However, IL15 is also anti-apoptotic and neurotrophic, and it suppresses nitric oxide production in neurons (Budagian et al., 2006). It is not yet clear whether its proinflammatory effects are beneficial for neuroregeneration, or whether the proinflammatory and anti-apoptotic effects represent two parallel processes in different courses of the associated disorders.

In contrast to the microglial changes related to innate immunity (LPS treatment), IL15-induced reactive astrocytes are implicated in MS. In demyelinating MS lesions, about 80–90% of astrocytes express IL15, whereas few astrocytes in normal control brain sections have detectable IL15; IL15 (+) microglia are more sparse and surrounded by infiltrating $CD8^+$ T cells. Cultured astrocytes show increased surface IL15 levels after treatment with proinflammatory cytokines, and promote cytotoxicity of co-cultured $CD8^+$ T lymphocytes. By contrast, a blocking antibody against IL15 abrogates the functional enhancements of the $CD8^+$ T cells (Saikali et al., 2010).

In sum, the intrathecal production of IL15 in the basal state is contributed to by both neurons and glia, and it provides neuroprotection with some regional specificity. The source of IL15 in the CNS includes both infiltrating and residential cells after inflammatory and autoimmune challenge; IL15 mainly serves as a proinflammatory cytokine. However, the detailed mechanisms of cell–cell interactions between IL15 (+) and IL15 receptor (+) cells are largely unexplored.

## 3. IL15 system at the blood–brain barrier (BBB): crosstalk between tumor necrosis factor α (TNF) and IL15

The unique functions of IL15 at the BBB were initially identified from studies with TNF. TNF is a ubiquitous cytokine entering the CNS by upregulated transport across the BBB that may modulate neuroregeneration after spinal cord injury (Pan et al., 1999; Pan and Kastin, 2001), hippocampal trauma (Pan et al., 2003), and stroke (Pan et al., 2006). Microarray analysis of RBE4 cerebral microvessel endothelial cells at different time intervals after TNF treatment showed that IL15 and IL15Rα are among the most robustly upregulated genes. TNF increases the expression of IL15Rα mRNA and protein, and accelerates the post-translational processing of IL15. TNF also modulates the expression of IL2Rβ and IL2Rγ, the other components of the IL15 receptor trimeric complex. The effects of TNF on the IL15 system are greater than the increases of the other cytokines, chemokines and cell adhesion molecules measured. The results indicate that IL15 is a novel mediator of TNF signaling at the level of the BBB, serving to amplify and modulate TNF signaling (Pan et al., 2009).

Consistently, IL15 induces NF-κB signaling in primary brain microvessel endothelial cells and cerebral endothelial cell lines, similar to the effect of TNF. Though the JAK/STAT signaling pathway is known to mediate most of the effects of IL15 shown in other cellular models, NFκB seems to play a larger role in BBB endothelia. IL15 induces transactivation of an NFκB luciferase reporter, and activation and nuclear translocation of the p65 subunit of NFκB, an effect delayed and attenuated in cerebral endothelia from IL15Rα knockout mice and inhibited by the IκB kinase inhibitor Bay 11-7082. The combined effect can potentially increase BBB permeability by decreased expression of the tight junction protein claudin-2 and modulate endocytosis and intracellular trafficking of a subset of