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# Interleukin 18 in the CNS

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**Abstract**

Interleukin (IL)-18 is a cytokine isolated as an important modulator of immune responses and subsequently shown to be pleiotropic. IL-18 and its receptors are expressed in the central nervous system (CNS) where they participate in neuroinflammatory/neurodegenerative processes but also influence homeostasis and behavior. Work on IL-18 null mice, the localization of the IL-18 receptor complex in neurons and the neuronal expression of decoy isoforms of the receptor subunits are beginning to reveal the complexity and the significance of the IL-18 system in the CNS. This review summarizes current knowledge on the central role of IL-18 in health and disease.

## Introduction

Interleukin (IL)-18 was isolated in 1995 as a co-factor that, in synergism with IL-12, stimulated the production of gamma interferon (INF-γ) in Th1 cells [1]. Since then extensive *in vitro* and *in vivo* studies have identified IL-18 as an important link between innate and adaptive immune responses and a regulator of both cellular and humoral immunity [2-4]. Constitutively produced as an inactive precursor by several cell types IL-18 is secreted in its active form following maturation by caspase 1 in response to inflammatory and infectious stimuli. In addition to its effects on Th1 cells, IL-18 is a strong stimulator of the activity of natural killer cells alone or in combination with IL-15, and of $CD8^+$ lymphocytes. Together with IL-2, IL-18 can also stimulate the production of IL-13 and of other Th2 cytokines. Thus, it is perhaps not surprising that IL-18 was found to be associated with or demonstrated to contribute to numerous inflammatory-associated disorders. These include infections, autoimmune diseases, rheumatoid arthritis, cancer, as well as metabolic syndrome and atherosclerosis [5-11].

IL-18 had not originally been expected to cross an intact blood brain barrier and its immunological effector cells are not normally found in the healthy brain. Yet, studies on the possible role of IL-18 in the central nervous system (CNS), initiated soon after its cloning, were prompted primarily by its similarities with IL-1, which was already demonstrated to have central action. It was soon found that IL-18 could be synthesized centrally and its receptor subunits were now demonstrated to be broadly expressed in neurons. When recombinant interleukin 18 became available it also became clear that IL-18 was active centrally. Work on mice null for IL-18 or its receptor subunit alpha is helping to decipher the action of this cytokine in the brain. Finally, the recent discovery of novel IL-18 receptor subunits in the brain has revealed the complexity of the IL-18 system and may lead to better understanding of both the similarities and opposing actions of IL-1 and IL-18. This review summarizes more than a decade of work aimed at understanding how the IL-18 system contributes to local central inflammatory processes or can influence neuronal function and behavior. A summary of the literature supporting the involvement of IL-18 in neurophysiological and neuropathological conditions is presented in Table 1.

### Components of the IL-18 system

IL-18 is synthesized as an inactive 24-kDa precursor protein that is subsequently processed by caspase-1 into its mature secretable form, which has a molecular weight of 18 kDa [4,12-16]. Pro-IL-18 can also be processed into its active form by various extracellular enzymes including protease 3 (PR-3), serine protease, elastase and cathepsin G [17-19]. Only the mature peptide is reported to be biologically active.

The existence of a putative short isoform of IL-18 resulting from alternative splicing removing 57 bp/19 aa was first described in rat adrenal glands (IL-18α) [20] and subsequently in mouse spleens (IL-18s) [21]. Recombinant IL-18s did not display IL-18-like activity in stimulating INF-γ production when tested alone but appeared

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