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Review article

The signal transduction mediated by erythropoietin and proinflammatory cytokines in the JAK/STAT pathway in the children with cerebral palsy

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Abstract

It is well established that erythropoietin (EPO) is a pleiotropic cytokine, which has a brain-derived neuroprotective effect in the central nervous system (CNS). Immune abnormality has a close relationship with cerebral palsy (CP), and may be even involved in the development of CP. There is evidence that the amount of EPO in CP children is lower than in normal children, but the levels of proinflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, are higher in the CP children. The signal transduction mediated by EPO that has a neuroprotective effect and mediated by proinflammatory cytokines that lead to brain damage shares the common JAK/STAT pathway. Under acute stress, the JAK/STAT pathway is occupied by massive proinflammatory cytokines, and the negative feedback inhibition factors like suppressor of cytokine signaling (SOCS) proteins are simultaneously activated, which exist in reciprocal inhibition to EPO in the JAK/STAT pathway. As a result, the signal transduction mediated by EPO is prevented or reduced, and the neuroprotective effect of EPO is eventually weakened. In this review, a novel approach to CP treatment through neurodevelopmental treatment (NDT) is put forward by analysis of the interrelationship of signal transduction mediated by EPO and proinflammatory cytokines in the JAK/STAT pathway and their roles in the development of CP, and some reasonable ideas for CP treatment are provided.

Keywords: Cerebral palsy; Erythropoietin; Inflammatory cytokines; JAK/STAT pathway; Neuro-endocrine-immune network; Neurodevelopmental treatment

1. Introduction

Cerebral palsy (CP) is the term for a range of non-progressive syndromes of posture and motor impairment that results from an insult to the developing central nervous system (CNS). It has been a challenge to define 'cerebral palsy' due to its coverage of heterogeneity of disorders. Advances in understanding of

Abbreviations: CP, cerebral palsy; CNS, central nervous system; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NT, neurotrophin; EPO, erythropoietin; IL-6, interleukin 6; TNF-α, tumor necrosis factor α; NDT, neurodevelopmental treatment; SOCS, suppressor of cytokine signaling; EPOR, erythropoietin receptor; JAK, Janus kinase; BBB, blood–brain barrier; VEGF, vascular endothelial growth factor; HIE, hypoxic–ischemic encephalopathy; CMV, cytomegalovirus; STAT, signal transducer and activator of transcription; GH, growth hormone; TPO, thrombopoietin; PI3PK, p85 subunit of phosphatidylinositol 3-kinase; NF-κB, nuclear factor-κB; MAPK, mitogen-activated protein kinase; LIF, leukemia inhibitor factor; PIAS, protein inhibitor of activated STAT; SHP, SH2 containing tyrosine phosphatase; KIR, kinase inhibitory region; IFN-γ, interferon-γ; HIF-1, hypoxia-inducible factor 1.

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development in infants with early brain damage, led Mutch and colleagues to define CP in 1992 as follows: 'an umbrella term covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development' [1]. This definition emphasized the motor impairment, acknowledged its variability, and excluded progressive disease. The worldwide prevalence and incidence of the disorder are not clearly known [2]. Although the molecular pathogenesis of CP is not completely understood, it is nowadays in many cases, the causes of brain injury are well documented. Other than many neurotrophic factors, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin (NT)-1, 3 and 4, which play important roles in the development of CP, this review will focus on the role of erythropoietin (EPO) and proinflammatory cytokines in the development of CP. In the review, we will briefly summarize the recent findings on the signal transduction mediated by EPO and proinflammatory cytokines and give an overview of their roles and its potential relevance in the development of CP.

1.1. Neuroprotective effect of EPO

EPO, a 165 amino acid (~30.4 kDa) glycoprotein hormone is a member of the cytokine type I superfamily [3]. EPO is initially produced in fetal liver, and then shifts to kidney during a short time after birth. It is initially believed that EPO acts exclusively on erythroid precursor cells [4]. However, recent evidences have shown that EPO is a pleiotropic cytokine plays non-hematopoietic roles, contributing to the development, maintenance, protection and renovation of the nervous system [5]. Indeed, brain, ovary, fallopian tube, uterus and testis can all secrete EPO [4,6]. The expression of EPO and erythropoietin receptor (EPOR) has been found in CNS, implicating that EPO has a neuroprotective effect in the CNS [7]. Immune abnormalities may be involved in the development of CP [8,9]. It had been demonstrated that the amount of EPO was decreased, and interleukin (IL)-6 and tumor necrosis factor (TNF)-α was simultaneously increased in CP children [10,11].

In CNS, EPO is mainly secreted by astrocytes, whereas EPOR is principally expressed in neurons [4]. Brain capillaries express EPOR abundantly through circulated EPO entering the brain [12]. EPO plays neuroprotective role in a large scale like neonatal hypoxia-ischemia [7], cerebral ischemia [13], and experimental autoimmune encephalitis [14]. Several direct-acting mechanisms by which EPO may protect neurons are inhibition of glutamate release, increase in desensitization of glutamate receptors and regulation of enzymes that scavenge oxygen radicals [15]. Indirectly, EPO may afford neuroprotection by stimulating angiogenesis, which increases the transport capability of oxygen-carrying blood and provides extra oxygen to brain and counteracts the effect of ischemia on neurons [16]. EPO also plays a direct or indirect role in inflammatory reaction, such as interfering in the inflammatory process, and reducing the expression of proinflammatory cytokines such as IL-6 and TNF-α [17]. Other studies have shown that EPO modulates nitric oxide synthesis especially within the vasculature [18], promotes neurotransmitter release [19,20] and neurotrophic action [21], prevents neuronal apoptosis [13] and antagonizes leakiness of the blood–brain barrier (BBB) by which induces the expression of vascular endothelial growth factor (VEGF) and anti-inflammation [22,23]. Therefore, EPO is an important component of the endogenous inducible neuroprotective mechanisms in CNS.

1.2. Effect of proinflammatory cytokines

Proinflammatory cytokines, such as IL-β1, IL-6 and TNF-α, have broad biological activity. They participate in the process of regulating the growth and differentiation of many histiocytes, and play important roles in immune and inflammatory reaction. They are also the main factors in the neuro-endocrine-immune network. The appropriate quantity of inflammatory cytokines promotes defense and injury repairing against diseases, but excessively makes an opposite effect. It has been found that their excessive expression plays an important role in the pathogenesis of CP [10]. However, the high level of proinflammatory cytokines is probably an independent risk factor for CP. Thus, in CINCA syndrome/NOMID which is a rare congenital inflammatory disorder characterized by a triad of neonatal onset of cutaneous symptoms, chronic meningitis and joint manifestation with recurrent fever and inflammation with hypersecretion of IL-1β and associated proinflammatory cytokines, patients do not develop CP.

Proinflammatory cytokines may cause brain damage through the following mechanisms [8,9,24–27]: (1) Promoting release of nitric oxide synthase, excitatory amino acids and free radicals. These substances have toxic effects on neurons, particularly on the development of brain. (2) Intrauterine infection. Proinflammatory cytokines activate the systemic inflammatory response, and further cause brain damage. (3) Causing white matter damage by increasing activity and gather of platelet and activating blood coagulation factors. (4) Destroying BBB. Peripheral harmful substances and inflammatory cytokines can enter brain and lead to brain damage. (5) Release of prostaglandin. It increases the risk of CP occurrence. In the children with hypoxic–ischemic encephalopathy (HIE) and CP, we found that CMV IgG is often positive or weakly positive, suggesting that the CP children have immunological abnormalities and