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Brain & Development 31 (2009) 503–509

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Review article

The role of hypoxia-inducible transcription factors in the hypoxic neonatal brain

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Received 14 December 2008; received in revised form 10 March 2009; accepted 12 March 2009

Abstract

Hypoxia-inducible transcription factors (HIF)-1 and HIF-2, composed of an oxygen-dependent α-subunit and a constitutive β-subunit, have been characterized as the most important regulators of oxygen homeostasis during physiological and pathological conditions. During embryonic, fetal and postnatal brain development, HIFs and specific HIF target genes are involved in early and highly active maturational processes by modulating cell differentiation, vascular development, angiogenesis and metabolic homeostasis. Under hypoxic conditions, activation of the HIF system reflects an immediate and cell-specific response to acute brain hypoxia. In a complementary fashion, both HIF-1 and HIF-2 modulate cerebral hypoxic stress responses and activate endogenous neuroprotective systems during acute and late stages of hypoxic/ischemic (HI) damage of the developing brain. Therefore, HIFs and their specific target genes that are expressed during brain injury are of particular interest for future diagnostic and therapeutic options in HI injury of the developing nervous system.

Keywords: Developing brain; Neuroprotection; VEGF; Mouse placenta; Hypoxic–ischemic encephalopathy

1. Introduction

Hypoxic and ischemic complications during the pre- and perinatal period are common causes of acquired neonatal brain damage associated with severe long-term neurodevelopmental disabilities. The broad spectrum of risk factors includes acute hypoxic/ischemic (HI) injury at birth arising from impaired materno-/feto-placental blood flow or acute anemia, as well as from chronically compromised prenatal fetal oxygen and energy supply, e.g. due to placental abnormalities or maternal diseases [1]. Resulting patterns of HI brain injury are periventricular lesions in the preterm newborn, and cortico-subcortical lesions, especially in the senso-motor cortex and the parasagittal region, and deep gray matter lesions of basal ganglia and thalamus in the near-term and term newborn [2]. This selective vulnerability of the brain to HI is mainly dictated by the stage of brain maturation and severity of hypoxia [3]. Inflammatory (e.g. IL-6, IL-1β, TNF-α), excitotoxic (e.g. glutamate, NMDA-R, AMPA-R) and apoptotic pathways are involved in the complex neurotoxic cascade following HI brain injury [3] and activate a process of self-sustaining secondary neurodegeneration in vulnerable CNS regions [4]. In addition, the availability of endogenous adaptive mechanisms modifying early and delayed stages of hypoxia-induced molecular cascade has been proposed as a crucial factor in the pathophysiology of HI damage of the developing brain. Among these adaptive systems, hypoxia-inducible transcription factors (HIFs) are of particular interest because of (a) their crucial adaptive role during immediate cerebral response to HI, and (b)

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doi:10.1016/j.braindev.2009.03.007

their ability to induce vasoactive and metabolic cytoprotective mechanisms during late stages of HI damage of the developing brain. These observations implicate HIFs as diagnostic and therapeutic options in HI injury of the developing nervous system.

2. Hypoxia-inducible transcription factors

Hypoxia-inducible transcription factors (HIF)-1 and HIF-2 have been characterized as the most important regulators of O_2-dependent gene transcription modulating oxygen and metabolic supply during hypoxia. HIFs are heterodimers of HIF-α (isoforms HIF-1α, HIF-2α, HIF-3α) and HIF-β (also termed ARNT, aryl hydrocarbon receptor nuclear translocator) subunits that all belong to the PAS family of basic helix–loop–helix (bHLH) transcription factors. Under normoxic conditions, HIF-α subunit is rapidly degraded by the ubiquitin–proteasome pathway mediated by specific prolyl residues. These residues are hydroxylated by HIF-prolyl hydroxylases (prolyl hydroxylation domain protein [PHD]), a process requiring di-oxygen and 2-oxoglutarate as co-substrates. Reduced activity of the PHDs under hypoxia initiates stabilization of the HIF-α subunit, heterodimerization with the β-subunit and activation of nuclear translocation that is followed by binding of the HIF heterodimer to hypoxia response elements of enhancers and promoters of specific target genes (Fig. 1). As a result, numerous HIF target genes modify oxygen and energy supply, e.g. by activation of glucose utilization (e.g. GLUT-1), vasoproliferative and vasoactive effects (e.g. vascular endothelial growth factor, VEGF; inducible NO synthase, iNOS) and cell survival (e.g. erythropoietin, EPO; insulin-like growth factor-1, IGF-1) (for review, see [5]). Interestingly, specific hypoxia response elements have been identified in the promoter region of HIF prolyl hydroxylases PHD2 and PHD3 inducing an autoregulatory feedback control that may prevent overstimulation of the HIF system during persisting hypoxia and reoxygenation [6]. The most widely expressed α-subunit is HIF-1α that was originally identified by affinity purification using oligonucleotides from the EPO locus [7]. As shown by knockout studies [8], HIF-1α and HIF-2α (also known as

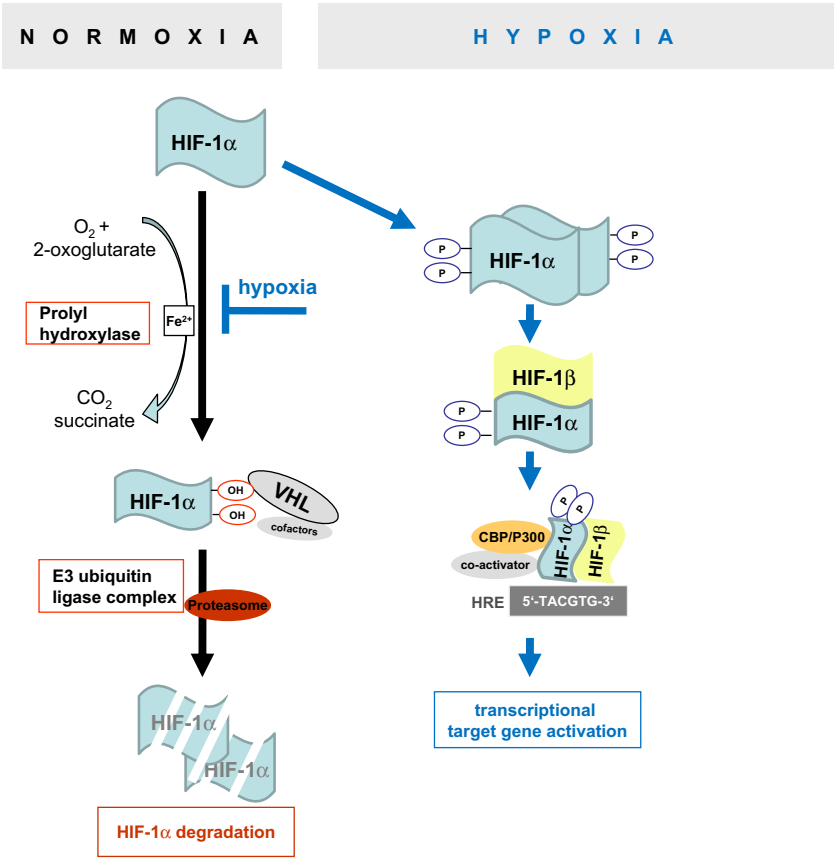

Fig. 1. HIF-1 stabilization and activity under normoxia and hypoxia. Under normoxic conditions, hydroxylation at specific proline residues leads to binding of HIF-1α to VHL followed by HIF-1α destruction via the ubiquitin/proteasome pathway. During hypoxia, HIF-1α subunit is stabilized and dimerizes with the ubiquitously expressed HIF-1β subunit. Activation of nuclear translocation is initiated followed by binding of the HIF-1 heterodimer to hypoxia response elements (HRE) of enhancers and promoters of specific target genes. *OH*, hydroxyl group; *VHL*, von Hippel-Lindau tumor suppressor protein; *P*, phosphorylated subunit.