ELSEVIER

Brain & Development xxx (2009) xxx–xxx

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

Regina Trollmann [a,*], Max Gassmann [b]

[a] Department of Pediatrics, Friedrich-Alexander-University of Erlangen-Nuremberg Loschgestrasse 15, 91054 Erlangen, Germany
[b] Institute of Veterinary Physiology, and Zurich Center for Integrative Human Physiology (ZIHP), University of Zurich, Switzerland

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)

* Corresponding author. Tel.: +49 9131 853 3101; fax: +49 9131 853 3389.
E-mail address: regina.trollmann@uk-erlangen.de (R. Trollmann).

0387-7604/$ - see front matter © 2009 Elsevier B.V. All rights reserved.
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

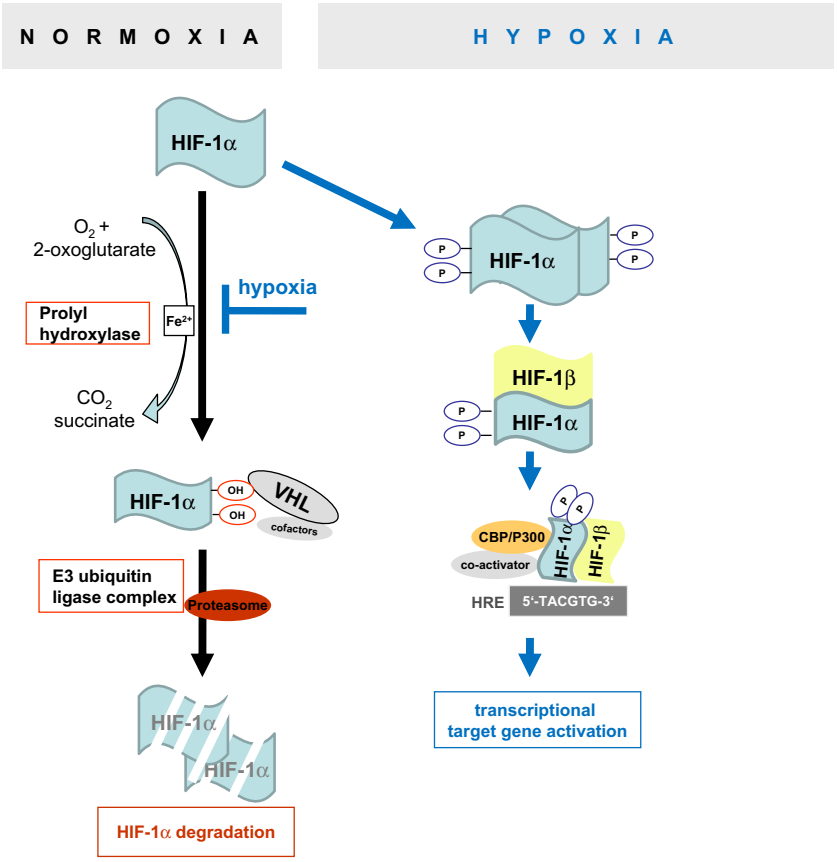

Fig. 1. HIF-1 stabilization and activity under normoxia and hypoxia. Under normoxic conditions, hydroxylation at specific proline residues leads to binding of HIF-1α to VHL followed by HIF-1α destruction via the ubiquitin/proteasome pathway. During hypoxia, HIF-1α subunit is stabilized and dimerizes 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.

Please cite this article in press as: Trollmann R, Gassmann M. The role of hypoxia-inducible transcription factors ..., Brain Dev (2009), doi:10.1016/j.braindev.2009.03.007

EPAS1, HOP2, HLF) have unique rather than redundant functions. Complementary action of the two α-subunits in the brain is further assumed e.g. by cell-type specific regulation and differences in target gene specificity [9–11]. For example, transcription of EPO during cerebral hypoxia is mainly regulated by HIF-2α, but not HIF-1α [9]. In contrast, transcriptional activity of genes encoding for enzymes of glycolytic pathway is under control of HIF-1α rather than HIF-2α [12].

Beside hypoxia, nitric oxide, metal ions (e.g. cobalt, nickel) and iron chelators (e.g. desferrioxamine) induce HIF-1α protein stabilization and transcriptional activity at the level of PHDs even under normoxic conditions [5]. Carbon monoxide induces tissue hypoxygenation by diminishing O_2-carrying capacity inhibiting HIF-α protein degradation *in vivo* as shown in adult rodent brain [11,13].

3. Role of HIFs during early brain development

During embryo- and organogenesis including brain development physiological hypoxia stimulates vascular development, angiogenesis and metabolic adaptation controlled by the HIF regulatory cascade [14,15]. During normal mouse brain development, hypoxic regions were detected from ED 8.5 to 9.0 in neuronal mesenchymal tissue associated with HIF-1α and VEGF co-localization [14]. HIF-1α protein detectable in normoxic developing mouse brain at GD 20 [16] and P7 [17] reflects persisting availability of HIF-1α in the regulation of physiological oxygen demands during neonatal period thereby ensuring fast and adequate adaptation to physiological fluctuations of cellular oxygen tension. Moreover, the crucial role of HIFs and HIF target genes for physiological vasculo- and angiogenesis and brain development is emphasized by knockout experiments. For example, HIF-1α knockout mouse embryos exhibit defects in neural development such as open neural tubes and abnormal cephalic vascularisation and lethality at ED 8.5 [8]. Embryonic brain defects in EPO and EPO-R null mice (lethality at around ED 13.5) consist of a thinning of the neuroepithelium, small brain size and incomplete closure of the neural tube [18].

4. Activation of the HIF system in hypoxic developing brain

Different experimental neonatal rodent models of hypoxic preconditioning [19,20], focal hypoxic/ischemic [19,21] and global non-ischemic hypoxic brain injury [16,17] demonstrated up-regulation of cerebral HIF proteins indicating their role in hypoxic stress-induced molecular responses of the developing nervous system. By establishing a mouse model of late-gestation intrauterine hypoxia in mice our group investigated endogenous HIF regulation during acute hypoxia (6% O_2 for 6 h) in the very immature mouse brain at the last day of mouse gestation (GD 20) [16] that approximately corresponds to the stage of brain maturation of a preterm newborn at mid-gestation [22]. Regional and cell-specific HIF-1α and HIF-2α protein accumulation due to hypoxia in developing mouse brain (Fig. 2) reflects immediate cerebral hypoxic stress responses in selectively vulnerable regions to hypoxia such as cerebral cortex, hippocampus and subventricular zone [4]. Cell-type specific regulation of HIF responses to brain hypoxia is evident from *in vitro* and *in vivo* studies, however, *in vivo* HIF response to hypoxia of the developing brain has not being extensively studied. In adult rodent brain, hypoxia induces stabilization and activity of HIF-1α protein in neurons, astrocytes, ependymal cells and endothelial cells [9,10,23], and HIF-2α protein in astrocytes, endothelial cells and Purkinje cells of the cerebellum [9,11]. Our studies performed at very early stage of mouse brain maturation (GD 20; Fig. 2) showed that HIF-1α is most prominently accumulated in cortical neurons and, to a lower extent, in glial cells and vascular endothelial cells of hippocampus and periventricular zone upon exposure to systemic hypoxia (6% O_2, 6 h). In contrast to a report on P6 rat brains undergoing hypoxic preconditioning (8% O_2; 3 h) [20], we showed cerebral HIF-2α induction upon exposure to hypoxia in the immature mouse brains. This data suggest a differential sensitivity of the HIF system that is attributable to developmental stage, duration and severity of hypoxia as well as cell type [9,12,20]. This is also the case for HIF target gene activation. At early stage of brain development (GD 20), especially VEGF seems to belong to the group of HIF target genes that are activated during early hypoxic response of the developing brain in contrast to EPO, GLUT-1 and iNOS [16,17]. Neuroprotective effects of VEGF have been shown *in vitro* and *in vivo* in postnatal rodent brain in response to ischemia and hypoxia [24,25]. VEGF is characterized as a neuronal survival factor by mediating both auto- and paracrine signaling functions in neurons *in vitro* [25] via its Flk-1 receptor and phosphorylation of downstream signaling molecules including MAPK, p90RSK, and STAT family members. Astrocyte-derived VEGF mediates survival and tube stabilization of hypoxic brain microvascular endothelial cells *in vitro* [26]. Thus, immediate induction of VEGF in developing hypoxic brain might contribute to hypoxic tolerance of neurons and astrocytes.

As to cell-specific target gene expression, *in vitro* hypoxia (8% O_2, 3 h) prominently induced e.g. VEGF, prolyl-4-hydroxylase α and 12-lipoxygenase in primary astrocytes rather than neurons, whereas adrenomedullin was strongly up-regulated in neurons but not astrocytes [20]. Of note, regulatory network mediating cerebral

Please cite this article in press as: Trollmann R, Gassmann M. The role of hypoxia-inducible transcription factors ..., Brain Dev (2009), doi:10.1016/j.braindev.2009.03.007

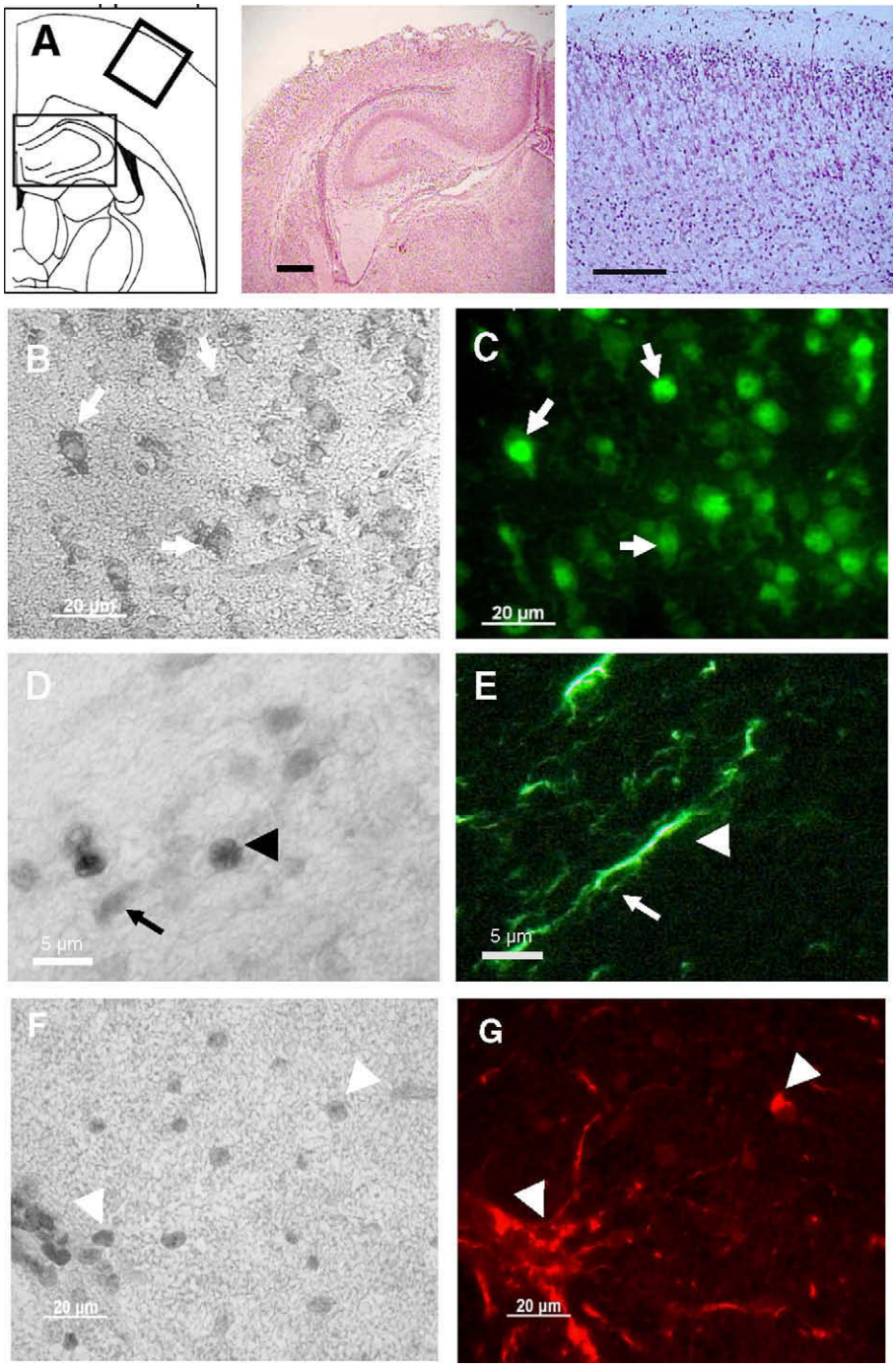

Fig. 2. Immunohistochemistry for HIF-1α and HIF-2α in developing mouse brain (gestational day 20) exposed to acute systemic hypoxia (6% O_2 for 6 h). (A) Coronal sections at the level of dorsal hippocampus are shown (A; *left*, overview; *middle*, hippocampus region, *right*, cerebral cortex; H.E.). Co-staining for HIF-1α (B) with NeuN (C) and HIF-1α (D) with GFAP (E) demonstrates hypoxia-induced accumulation of HIF-1α in neurons of the cerebral cortex, and, to a lower extent, in glial cells (note that scale bars in C and D are 5 µm). In contrast, HIF-2α (F) co-stained with GFAP (G) was induced in glial cells of the hippocampus region (F and G) but not in neurons (data not shown). Adapted from Trollmann et al. [16].

oxygen homeostasis involves a variety of transcription factors others than HIFs, such as NF-κB, EGF, insulin signaling pathways and transcriptional regulators Myc, Jun, and p53, modifying glucose metabolism, angiogenic growth factors, cytokines as well as pro-apoptotic factors [12].

5. HIFs as early markers of developing brain hypoxia

Prognostic markers which reliably identify neonates for cerebral HI injury during the first postnatal hours, when neuroprotective therapies might be efficient, are limited [27]. As response of HIFs to changes in cellular

Please cite this article in press as: Trollmann R, Gassmann M. The role of hypoxia-inducible transcription factors ..., Brain Dev (2009), doi:10.1016/j.braindev.2009.03.007

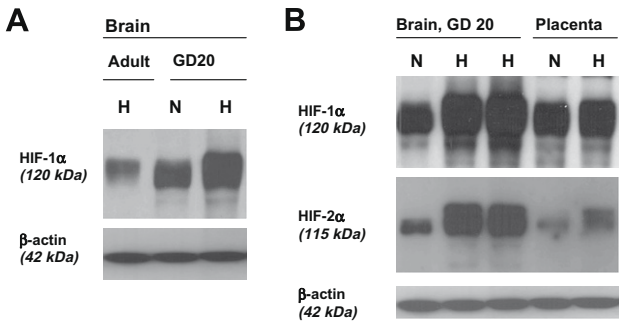

Fig. 3. Western blot analysis of HIF-1α and HIF-2α protein in developing mouse brain and placenta upon exposure of the pregnant mother to normoxia (N) or hypoxia (H; 6% O_2, 6 h) at GD 20. Both α-subunits were detectable in normoxic brains (A and B) and placentas (B). Of note, analysis of a hypoxic adult brain (A, lane 1) showed a less intense HIF-1α band than a normoxic fetal brain (A, compare lanes 1 and 2). In response to acute hypoxia, HIF-1α and HIF-2α protein stabilization is strongly induced in both developing brain and placenta. Adapted from Trollmann et al. [16].

oxygen tension is immediate, these factors represent promising markers to signal relevant tissue hypoxia. Interestingly, human *in vivo* studies suggested adrenomedullin and VEGF as early indicators of perinatal brain injury in preterms [28] and term asphyxiated newborns [29,30]. Moreover, several HIF-regulated growth factors measured in cord blood and placenta have been identified to indicate acute or chronic perinatal hypoxia in term newborns [31,32]. Based on existing cell biological data elucidating molecular pathways involved in the immediate responses of the developing brain to hypoxia *per se*, and considering our mouse model of acute antepartum systemic hypoxia [16] we propose that HIFs and specific target genes represent indicators of cerebral hypoxic distress during acute hypoxia. Specifically, systemic hypoxia at GD 20 induced a simultaneous up-regulation of HIF-1α and HIF-2α in developing mouse brain and placenta implying that placental accumulation of HIFs is indicative for fetal cerebral hypoxic distress (Fig. 3). Of note, acute hypoxia differentially affected transcriptional activity of specific HIF target genes in placenta and brain indicating time- and cell-specific sensitivity of HIF target genes to hypoxia [16] that might have future diagnostic implications. Interestingly, experimental data supported previous observations of increased VEGF expression in human placentas of asphyxiated newborns developing severe hypoxic–ischemic encephalopathy compared to controls [30].

6. HIFs and neuroprotective strategies

Bergeron et al. [23] described protection of adult rodent brain against experimental stroke by "hypoxic preconditioning" which is defined as exposure of rodents to systemic non-lethal hypoxia (8% O_2 for 3 h) before the ischemic event. This "ischemic tolerance" similarly observed due to preconditioning by desferrioxamine and cobalt chloride in adult brain [23] and retina [33] as well as in neonatal rodent brain [19] has been proposed to be the result of HIF-1 and HIF target gene activation (e.g. VEGF, EPO, adrenomedullin). Among these protective target genes, especially EPO has been extensively investigated in terms of its therapeutic use to reduce stroke volume and improve functional outcome after neonatal stroke in rodents. Neuroprotection by recombinant EPO (rEPO) includes many pathways such as diminishing apoptosis by activation of anti-apoptotic proteins bcl-2 and bcl-XL and inhibition of pro-apoptotic caspases, inflammation, excitotoxicity and activation of brain derived neurotrophic factor [34,35]. Moreover, processes of late brain recovery after HI injury are modulated by EPO such as neurogenesis, angiogenesis and migration of regenerating neurons (for review, see [36]). Protective effects have even been found if high-dose rEPO treatment was initiated after the onset of HI injury in neonatal rodents [34]. Human data on neuroprotective effects of rEPO in hypoxic neonatal brain injury is limited. Studies initiated for treatment of anemia showed no significant improvement of neurodevelopmental outcome in preterm neonates who received low-dose rEPO [37]. A recent randomized mono-center study on efficacy and safety of high-dose rEPO treatment in premature infants revealed no significant effects on short-term outcome, however, of importance, no significant adverse effects [38]. Neurobiological characteristics of EPO/EPO-R system during development might explain differences of *in vitro* and *in vivo* effects such as limited transport across blood–brain-barrier and delayed hypoxia-induced activation of the heterodimeric low affinity EPO-R [36].

The hypothesis arises as whether it is advantageous to target HIFs for neuroprotection as activation of the broad spectrum of HIF target genes might have synergistic protective effects. Indeed, embryonic neuronal cell culture experiments [39] showed that inhibitors of PHD significantly prevented glutamate-induced neuronal death suggesting PHD as promising targets for protection from oxidative death in neurons.

In summary, at early developmental stage of brain maturation, HIFs well characterized as complementary systems to modulate hypoxic stress responses reflect an immediate and cell-specific response to acute brain hypoxia. Based on experimental data, HIFs and HIF target genes are promising candidates for potential future diagnostic and prognostic marker systems in perinatal HI encephalopathy. Addressing both cellular and regional vulnerability of the developing brain pharmacological activation of HIF-regulated mechanisms might reflect targets for future studies on age-appropriate neuroprotection in newborns.

Please cite this article in press as: Trollmann R, Gassmann M. The role of hypoxia-inducible transcription factors ..., Brain Dev (2009), doi:10.1016/j.braindev.2009.03.007

Acknowledgements

This work was supported by Deutsche Forschungsgemeinschaft Grant TR 726/2-1 (to R.T.) and the Swiss National Science Foundation (to M.G.).

References

[1] Terzidou V, Bennet P. Maternal risk factors for fetal and neonatal brain damage. Biol Neonate 2001;79:157–62.
[2] Rutherford M, Srinivasan L, Dyet L, Ward P, Allsop J, Counsell S, et al. Magnetic resonance imaging in perinatal brain injury: clinical presentation, lesions and outcome. Pediatr Radiol 2006;36:582–92.
[3] Jensen FE. Developmental factors regulating susceptibility to perinatal brain injury and seizures. Curr Opin Pediatr 2001;18:628–33.
[4] Northington FJ, Ferriero DM, Flock DL, Marin LJ. Delayed neurodegeneration in neonatal rat thalamus after hypoxia-ischemia is apoptosis. J Neurosci 2001;21:1931–8.
[5] Fandrey J, Gorr TA, Gassmann M. Regulating cellular oxygen sensing by hydroxylation. Cardiovasc Res 2006;71:642–51.
[6] D'Angelo G, Duplan E, Boyer N, Vigne P, Frelin C. Hypoxia up-regulates prolyl hydroxylase activity: a feedback mechanism that limits HIF-1 responses during reoxygenation. J Biol Chem 2003;278:38183–7.
[7] Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic helix–loop–helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci USA 1995;92:5510–4.
[8] Iyer NV, Kotch LE, Agani F, Leung SW, Laughner E, Wenger RH, et al. Cellular and developmental control of O_2 homeostasis by hypoxia inducible factor 1α. Genes Dev 1998;12:149–62.
[9] Chavez JC, Baranova O, Lin J, Pichiule P. The transcriptional activator hypoxia inducible factor 2 (HIF-2/EPAS-1) regulates the oxygen-dependent expression of erythropoietin in cortical astrocytes. J Neurosci 2006;26:9471–81.
[10] Stroka DM, Burkhardt T, Desbaillets I, Wenger RH, Neil DAH, Bauer C, et al. HIF-1 is expressed in normoxic tissues and displays an organ-specific regulation under systemic hypoxia. FASEB J 2001;15:2445–53.
[11] Wiesener MS, Jurgensen JS, Rosenberger C, Scholze CK, Horstrup JH, Warnecke C, et al. Widespread hypoxia-inducible expression of HIF-2alpha in distinct cell populations of different organs. FASEB J 2003;17:271–3.
[12] Mense SM, Sengupta A, Zhou M, Lan C, Bentsman G, Volsky DJ, et al. Gene expression profiling reveals the profound upregulation of hypoxia-responsive genes in primary human astrocytes. Physiol Genomics 2006;25:435–49.
[13] Bani Hashemi S, Braun J, Bernhardt WM, Rascher W, Dötsch J, Trollmann R. HIF-1alpha subunit and vasoactive HIF-1-dependent genes are involved in carbon monoxide-induced cerebral hypoxic stress response. Eur J Appl Physiol 2008;104:95–102.
[14] Lee YM, Jeong CH, Koo SY, Son MJ, Song HS, Bae SK, et al. Determination of hypoxic region by hypoxia marker in developing mouse embryos in vivo: a possible signal for vessel development. Dev Dyn 2001;220:175–86.
[15] Yu X, Shacka JJ, Eells JB, Suarez-Quian C, Przygodzki RM, Beleslin-Cokic B, et al. Erythropoietin receptor signaling is required for normal brain development. Development 2002;129:505–16.
[16] Trollmann R, Strasser K, Keller S, Antoniou X, Grenacher B, Ogunshola OO, et al. Placental HIFs as markers of cerebral hypoxic distress in fetal mice. Am J Physiol Regul Integr Comp Physiol 2008 [epub ahead of print].
[17] Trollmann R, Schneider J, Keller S, Strasser K, Wenzel D, Rascher W, et al. HIF-1-regulated vasoactive systems are differentially involved in acute hypoxic stress responses of the developing brain of newborn mice and are not affected by levetiracetam. Brain Res 2008;1199:27–36.
[18] Knabe W, Knerlich F, Washausen S, Kietzmann T, Siren AL, Brunnett G, et al. Expression patterns of erythropoietin and its receptor in the developing midbrain. Anat Embryol 2004;207:503–12.
[19] Bergeron M, Gidday JM, Yu AY, Semenza GL, Ferriero DM, Sharp FR. Role of hypoxia-inducible factor-1 in hypoxia-induced ischemic tolerance in neonatal rat brain. Ann Neurol 2000;48:285–96.
[20] Bernaudin M, Tang Y, Reilly M, Petit E, Sharp FR. Brain genomic response following hypoxia and re-oxygenation in the neonatal rat. J Biol Chem 2002;277:39728–38.
[21] Van den Tweel ER, Kavelaars A, Lombardi MS, Nijboer CH, Groenendaal F, van Bel F, et al. Bilateral molecular changes in a neonatal rat model of unilateral hypoxic–ischemic brain damage. Pediatr Res 2006;59:434–9.
[22] Dobbing J, Sands J. Comparative aspects of the brain growth spurt. Early Hum Dev 1979;3:79–83.
[23] Bergeron M, Yu AY, Solway KE, Semenza GL, Sharp FR. Induction of hypoxia-inducible factor-1 (HIF-1) and its target genes following focal ischaemia in rat brain. Eur J Neurosci 1999;11:4159–70.
[24] Sun Y, Jin K, Xie L, Childs J, Mao XO, Logvinova A, et al. VEGF-induced neuroprotection, neurogenesis, and angiogenesis after focal cerebral ischemia. J Clin Invest 2003;111:1843–51.
[25] Ogunshola OO, Antic A, Donoghue MJ, Fan SY, Kim H, Stewart WB, et al. Paracrine and autocrine functions of neuronal vascular endothelial growth factor (VEGF) in the central nervous system. J Biol Chem 2002;277:11410–5.
[26] Chow J, Ogunshola O, Fan SY, Li Y, Ment LR, Madri JA. Astrocyte-derived VEGF mediates survival and tube stabilization of hypoxic brain microvascular endothelial cells in vitro. Brain Res Dev Brain Res 2001;130:123–32.
[27] Thorngren-Jerneck K, Alling C, Herbst A, Amer-Wahlin I, Marsal K. S100 protein in serum as a prognostic marker for cerebral injury in term newborn infants with hypoxic ischemic encephalopathy. Pediatr Res 2004;55:406–12.
[28] Gazzolo D, Marinoni E, Giovannini L, Letizia C, Serra G, Di Iorio R. Circulating adrenomedullin is increased in newborns developing intraventricular hemorrhage. Pediatr Res 2001;50:544–7.
[29] Di Iorio R, Marinoni E, Lituania M, Serra G, Letizia C, Cosmi EV, et al. Adrenomedullin increases in term asphyxiated newborns developing intraventricular hemorrhage. Clin Biochem 2004;37:1112–6.
[30] Trollmann R, Amann K, Schoof E, Beinder E, Wenzel D, Rascher W, et al. Hypoxia activates human placental VEGF system in vitro and in vivo: up-regulation of placental VEGF system in clinically relevant hypoxic ischemia in birth asphyxia. Am J Obstet Gynecol 2003;188:517–23.
[31] Marchini G, Hagenäs L, Kocoska-Maras L, Berggren V, Hansson LO. Insulin-like growth factor binding protein-1 and interleukin-6 are markers of fetal stress during parturition at term gestation. J Pediatr Endocrinol Metab 2005;18:777–83.
[32] Trollmann R, Klingmüller K, Schild RL, Rascher W, Dötsch J. Differential gene expression of somatotrophic and growth factors in response to in vivo hypoxia in human placenta. Am J Obstet Gynecol 2007;197(601):e1–6.
[33] Grimm C, Wenzel A, Acar N, Keller S, Seeliger M, Gassmann M. Hypoxic preconditioning and erythropoietin protect retinal neurons from degeneration. Adv Exp Med Biol 2006;588:119–31.
[34] Sun Y, Calvert JW, Zhang JH. Neonatal hypoxia/ischemia is associated with decreased inflammatory mediators after erythropoietin administration. Stroke 2005;36:1672–8.

Please cite this article in press as: Trollmann R, Gassmann M. The role of hypoxia-inducible transcription factors ..., Brain Dev (2009), doi:10.1016/j.braindev.2009.03.007

[35] Viviani B, Bartesaghi S, Corsini E, Villa P, Ghezzi P, Garau A, et al. Erythropoietin protects primary hippocampal neurons increasing the expression of brain-derived neurotrophic factor. J Neurochem 2005;93:412–21.

[36] Noguchi CT, Asavaritikrai P, Teng R, Jia Y. Role of erythropoietin in the brain. Crit Rev Oncol Hematol 2007;64:159–71.

[37] Bierer R, Peceny MC, Hartenberger HC, Ohls RK. Erythropoietin concentrations and neurodevelopmental outcome in preterm infants. Pediatrics 2006;118:e635–40.

[38] Fauchère JC, Dame C, Vonthein R, Koller B, Arri S, Wolf M, et al. An approach to using recombinant erythropoietin for neuroprotection in very preterm infants. Pediatrics 2008;122:375–82.

[39] Siddiq A, Ayoub IA, Chavez JC, Aminova L, Shah S, LaManna JC, et al. Hypoxia-inducible factor prolyl 4-hydroxylase inhibition. A target for neuroprotection in the central nervous system. J Biol Chem 2005;280:41732–43.

Please cite this article in press as: Trollmann R, Gassmann M. The role of hypoxia-inducible transcription factors ..., Brain Dev (2009), doi:10.1016/j.braindev.2009.03.007