

REVIEW

Hypoxia-inducible factors and the prevention of acute organ injury

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This article is one of eleven reviews selected from the *Annual Update in Intensive Care and Emergency Medicine 2011* (Springer Verlag) and co-published as a series in *Critical Care*. Other articles in the series can be found online at <http://ccforum.com/series/annual>. Further information about the *Annual Update in Intensive Care and Emergency Medicine* is available from <http://www.springer.com/series/8901>

Introduction

Hypoxic preconditioning has long been considered as organ-protective, and its clinical usage has been suggested in elective procedures, such as coronary surgery and organ transplantation. Although the mechanisms have not been clearly elucidated, it has been postulated that changes in cell-membrane composition and upregulation of various cellular protective mechanisms are responsible for a better tolerance of acute injury. Remote preconditioning (i.e., hypoxic stress in one organ conferring resistance to acute hypoxia in other organs) suggests organ cross-talk, perhaps mediated by cytokines and the immune system.

Increased expression of heme-oxygenase (HO)-1, heat-shock proteins (HSP), growth factors such as vascular endothelial factor (VEGF), and erythropoietin (EPO) are among the numerous adaptive responses to sublethal injury that are believed to participate in tissue tolerance during subsequent stress. EPO, for instance, is a ubiquitous pleiotropic survival and growth factor that attenuates experimental acute injury in various organ systems, including neuronal, retinal, cardiac, renal, and hepatic tissues. Its clinical efficacy, though suggested in critically ill patients, is yet to be defined [1].

The expression of these protective mediators and many others is regulated by hypoxia-sensing mechanisms through the induction and stabilization of so called hypoxia-inducible factors (HIF) [2]. In this chapter, we will outline the control and action of HIF as key regulators of hypoxic adaptive response, and particularly examine HIF expression during hypoxic stress. We shall discuss recently developed measures that enable HIF

signal modification and describe their potential use in conferring tissue tolerance during incipient organ injury.

HIF regulation and action

HIFs are heterodimers (Fig. 1), composed of a constitutive β -subunit (HIF- β) and one of three different oxygen-dependent and transcriptionally active α -subunits, among which HIF-1 α and -2 α are acknowledged as promoters of hypoxia adaptation, whereas the role of HIF-3 α remains unclear. Under normoxia, HIF- α subunits are constantly produced, but not allowed to accumulate, since they are rapidly hydroxylated by oxygen-dependent HIF prolyl-4-hydroxylase domain enzymes (PHD), subsequently captured by the ubiquitin ligase Von-Hippel-Lindau protein (VHL), and degraded by the proteasome. Under oxygen deficiency, PHD activity is reduced, HIF- α accumulates within the cytosol, $\alpha\beta$ -dimers are formed, translocate into the nucleus, and bind to hypoxia response elements (HREs) in the promoter enhancer region of genes, which are subsequently transactivated [2–4].

The biological effects of the more than 100 acknowledged HIF target genes are multiple, and include key steps in cell metabolism and survival. Many of the HIF-target genes constitute a reasonable adaptation to hypoxia, such as erythropoiesis (EPO), increased glucose uptake (glucose transporter-1), switch of metabolism to glycolysis (several key enzymes of glycolysis), increased lactate utilization (lactate dehydrogenase), angiogenesis (VEGF), vasodilation (inducible nitric oxide synthase [iNOS]), removal of protons (carbonic anhydrase 9), and scavenging of free radicals (HO-1) [2–4].

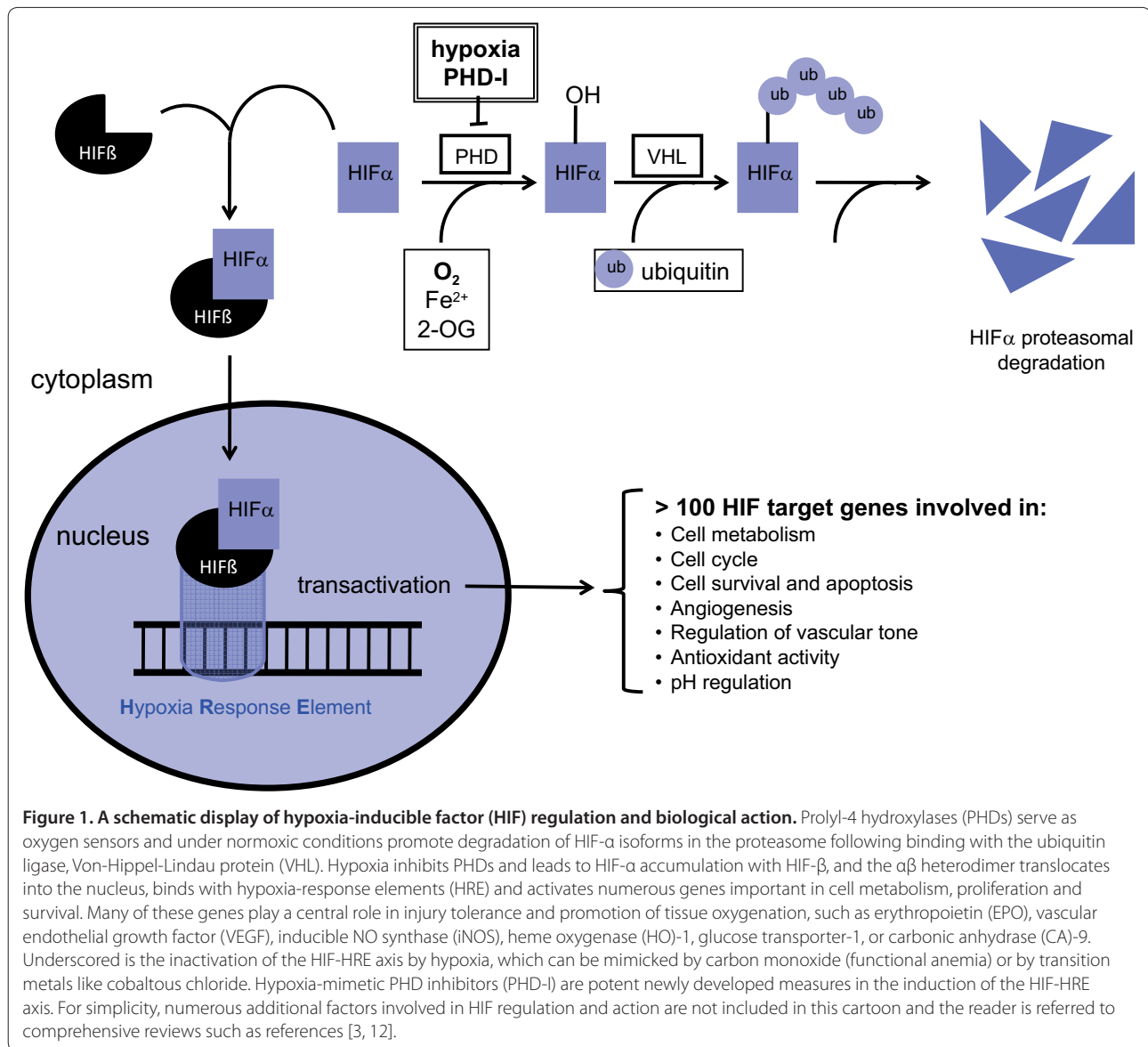
Biological and therapeutic modes of HIF activation

Every cell type has the potential to upregulate HIF, principally by the inhibition of PHD, under conditions when cellular oxygen demand exceeds oxygen supply,

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namely under cellular hypoxia. However, the threshold and extent of HIF activation may depend on the hypoxic stimulus and cell type involved. To some extent, these cellular variations may reflect different expression of various PHD isoforms in different tissues [5–7].

As HIF stimulation may potentiate hypoxia tolerance, studies were conducted to explore its clinical application. Widespread experimental hypoxic stimuli are listed in Table 1, all acting principally by the control of HIF- α degradation, initiated by PHDs. Except for carbon monoxide exposure, which is currently being tested in patients, none of these stimuli seems suitable for preconditional HIF activation in humans.

Apart from hypoxic stabilization, widely proven *in vivo*, HIF activation has also been demonstrated to occur

under normal ambient oxygen tensions, mostly in cell cultures challenged with cytokines and growth factors. However, under stress, oxygen demand likely is increased, thus possibly leading to intracellular hypoxia even in cells kept under room air. For technical reasons, it is probably impossible to rule out such local cellular hypoxia that may exist predominantly within the mitochondria. Beyond this academic distinction between true cellular hypoxia and normoxia, it is important to recognize that clinical conditions, like inflammation, infection and sepsis, may lead to HIF activation. Thus, theoretically, cytokines or growth factors could be used for preconditional HIF activation in humans.

Although not a reasonable therapeutic intervention, strong and stable normoxic HIF activation can be

Table 1. Modes of HIF signal enhancement

Stimulus/Agent	Remarks	Potential Clinical Applications
Inhibition of PHDs by the induction of cellular physiologic hypoxia		
Hypoxic chamber (e.g., 8% O ₂ in ambient air)	depressed systemic PO ₂	
Carbon monoxide admixture to ambient air	functional anemia normal systemic PO ₂	✓
Anemia		normal systemic PO ₂
Arterial clamping		normal systemic PO ₂
Chemical inhibition of PHDs by hypoxia-mimetics		
CoCl ₂ (interferes with Fe ²⁺)	non-specific	
Mimosine (2-oxoglutarate analogue)	non-specific	
Other patented PHD inhibitors	specific	✓
Molecular biology techniques		
Von-Hippel-Lindau knockout	non-specific	
PHD siRNA transfection	PHD-specific	
Constitutively active HIF-α transgenes	organ-specific	✓

PHD: prolyl hydroxylase domain enzyme

achieved by deletion of the VHL gene, which is a constant phenomenon in Von Hippel Lindau Disease and in renal clear cell carcinoma, and is also encountered in other tumors. Transgenic animals with VHL knockout serve to test the potential of HIF activation in ischemic/hypoxic diseases (C Rosenberger, unpublished data) [8]. Additional experimental probes for enhancing HIF signal are by transfection with PHD siRNA [9] or with the generation of constitutively active HIF-α transgenes [10].

So-called hypoxia mimetics block PHD activity, thus upregulating HIF under normoxia. PHDs require 2-oxoglutarate and ferrous iron as co-substrates. Non-specific PHD inhibitors are either 2-oxoglutarate analogues or interfere with Fe²⁺. Recently, more specific PHD inhibitors (PHD) have been synthesized [11], and are currently being tested in animal and human studies.

Figure 1 represents a simplistic scheme of the canonical HIF regulation and action. Recent discoveries underscore a host of additional compound biological pathways, associated with the regulation of the HIF signal, including the control of HIF synthesis, HIF controlling PHD synthesis, putative competing/intervening impacts of HIF-3α and PHD-3, cross-talk of HIF and other key regulators of gene expression (STAT, p-300 and others), further modification of HIF-α activity at the level of DNA hypoxia-responsive elements by small ubiquitin-like modifiers (SUMO) and factor inhibiting HIF (FIH), and the effect of reactive oxygen species (ROS), NO and Krebs cycle metabolites on HIF degradation. These complex pathways are beyond the scope of this review, and the interested reader is referred to additional references [3,5,12–18].

HIF expression under hypoxic stress and tissue injury

The kidney serves as an excellent example for understanding HIF expression under hypoxic stress. Renal

oxygenation is very heterogeneous, with PO₂ falling to levels as low as 25 mmHg in the outer medulla under normal physiologic conditions and to even lower values in the papilla [3,4,19]. Changes in renal parenchymal microcirculation and oxygenation have been thoroughly investigated in acute and chronic renal disorders [19,20]. Finally, the complex renal anatomy in which different cell types are in close proximity to regions with comparable ambient oxygenation, enables comparisons of cellular HIF response.

Interestingly, HIF expression is below detection threshold by immunostaining in the renal medulla, despite low physiologic ambient oxygenation (It should be emphasized that this statement regarding negative HIF immunostaining in the normally hypoxic medulla relates to kidneys perfusion-fixed in vivo without an interruption of renal oxygenation before fixation. Other modes of tissue harvesting for HIF determination, either by immunostaining or by molecular biology techniques may be falsely positive, as hypoxia-induced inhibition of PHD activity is instantaneous, and may lead to HIF-α stabilization even over short periods of hypoxia). Conceivably, this reflects the plasticity of HIF control to adjust for 'physiologically normal' oxygenation (i.e., adjusted rates of HIF-α generation and degradation under normal conditions).

Enhanced renal HIF-α is noted in rodents subjected to hypoxia or to inhaled carbon monoxide (chemical hypoxia) [21], and in hypoxic isolated perfused kidneys [22]. Different cells express diverse HIF isoforms: Whereas tubular segments express HIF-1α, HIF-2α is principally produced by vascular endothelial and interstitial cells [21–23]. Interestingly, HIF-dependent genes are also selectively expressed in different cell types. For instance HIF-2-triggered EPO generation is specifically found in interstitial cells in the deep cortex [24]. In hypoxic

isolated perfused kidneys, attenuation of severe medullary hypoxia by the inhibition of tubular transport markedly enhanced HIF expression, probably underscoring a window of opportunity to generate HIF and HIF-mediated adaptive responses only under moderate and sublethal hypoxic stress [22]. This pattern is consistent with HIF expression at the border of renal infarct zones only, indicating that dying cells within the critically ischemic region are incapable of mounting a hypoxia adaptive response [25].

We also found that HIF- α isoforms are stabilized in acute hypoxic stress, predominantly in the cortex in rhabdomyolysis-induced kidney injury [26], in the outer stripe of the outer medulla following ischemia and reperfusion [27,28], or in the inner stripe and inner medulla following the induction of distal tubular hypoxic injury by radiocontrast agent, or after the inhibition of prostaglandin or NO synthesis or with their combinations [23]. Outer medullary HIF stabilization is also noted in chronic tubulointerstitial disease [29] and in experimental diabetes [30], again spatially distributed in areas with proven hypoxia. HIF was also detected in biopsies from transplanted kidneys [31]. Thus, HIF immunostaining is chronologically and spatially distributed in renal regions with abnormally low PO₂.

Normal mice subjected to warm ischemia and reperfusion display limited injury only, as compared with extensive damage in HIF (+/-) mice [32]. Thus, the importance of mounting an HIF response during hypoxic stress is undeniable.

Hypoxia-driven HIF stabilization during hypoxic stress has been encountered in other organs as well. HIF-1 α and PHD-2 expression increased in the neonatal rat brain following hypoxia [33] and HIF was detected in the hypoxic subendocardium [34] and in the ischemic liver [27]. HIF is also found within hypoxic regions in tumors, and may play an important role in tumor progression via upregulation of growth promoting and angiogenic factors [35].

Potential usage of HIF modulation in clinical practice

The impact of HIF stimulation on the expression of HIF-dependent tissue-protective genes led to the expectation that timely upstream HIF stimulation may have great potential in the protection of endangered organs by downstream induction of protective genes [12]. Indeed, repeated systemic hypoxia, for instance, results in enhanced expression of renal HIF and HIF-dependent genes and attenuates warm-ischemic injury [36].

The use of hypoxia-mimetic PHD inhibitors is a promising potential new treatment option in diseases such as myocardial infarction, stroke, renal or liver injury, peripheral vascular disease, or severe anemia. Studies

with PHD inhibitors and other manipulations of HIF upregulation favor this hypothesis [11].

Anemia

Specific PHD inhibitors induce HIF-2 α expression in interstitial fibroblasts in the deep cortex [24], enhance erythropoietin generation, and were found to provoke erythrocytosis in primates [37]. Phase 2 clinical trials in patients with chronic kidney disease are currently under way, studying the effect of oral PHD inhibitors as potential substitutes to EPO injection.

Acute kidney injury

The potential protective impact of HIF upregulation by PHD inhibitors has been extensively studied in acute kidney injury. In isolated kidneys perfused with low-oxygen containing medium, pre-treatment with a PHD inhibitor improved renal blood flow and attenuated medullary hypoxic damage [38]. Conditional inactivation of VHL in mice (hence HIF stabilization) resulted in tolerance to renal ischemia and reperfusion [8] and to rhabdomyolysis-induced acute kidney injury (Rosenberger C, unpublished data). Whereas gene transfer of negative-dominant HIF led to severe damage in the normally hypoxic renal medulla in intact rats, transfer of constitutively active HIF (HIF/VP16) induced expression of various HIF-regulated genes and protected the medulla against acute ischemic insults [39]. Furthermore, in rats and mice subjected to warm ischemia and reflow, PHD inhibitors and carbon monoxide pre-treatment (i.e., functional anemia) markedly attenuated kidney damage and dysfunction [32,40]. Donor pre-treatment with a PHD inhibitor also prevented graft injury and prolonged survival in an allogenic kidney transplant model in rats [41]. Finally, rats preconditioned by carbon monoxide, displayed reduced cisplatin renal toxicity, with attenuation of renal dysfunction and the extent of tubular apoptosis and necrosis [42]. Taken together, all these observations indicate that HIF stabilization seemingly is a promising novel interventional strategy in acute kidney injuries [12].

Myocardial injury

Activation of the HIF system has also been found to be cardioprotective. In a model of myocardial ischemia in rabbits, pre-treatment with a PHD inhibitor induced robust expression of HO-1 and markedly attenuated infarct size and myocardial inflammation [43]. In another report, PHD inhibitors did not reduce infarct size, but improved left ventricular function and prevented remodeling [44]. In the same fashion, selective silencing of PHD-2 with siRNA 24 h before global myocardial ischemia/reperfusion in mice reduced the infarct size by 70% and markedly improved left ventricular systolic

function [9]. Remote preconditioning by intermittent renal artery occlusion also resulted in cardiac protection, conceivably through PHD inhibition [45].

Enhanced levels of PHD-3 were traced in the hibernating myocardium [34] and in end-stage heart failure in humans, associated also with elevated HIF-3 α [46] (which may act as a competitive inhibitor of active HIF- α isoforms [14]). Thus, PHD inhibitors may conceivably also be beneficial in these disorders. Finally, cardioprotection during heat acclimation is also mediated in part by HIF upregulation [47], providing another potential situation for the administration of PHD inhibitors.

Neuronal injuries

The effect of PHD inhibitors has also been assessed in disorders of the central nervous system. *In vitro*, rotenone-induced neuronal apoptosis was attenuated and autophagy increased, as the result of enhanced HIF following deferoxamine administration [48]. *In vivo*, PHD inhibitors have shown promising results in the attenuation of ischemic stroke [49], and might be neuroprotective in metabolic chronic neurodegenerative conditions [50]. However, studies showing inhibition of PHD-1 by ROS suggest non-HIF-mediated neuronal protection under normoxic conditions [51].

Lung injury

Preterm lambs developing respiratory distress syndrome display upregulation of PHDs with a reciprocal fall in HIF- α isoforms and HIF-dependent VEGF [53]. This observation implies that PHD inhibitors might have therapeutic potential in this clinical setup.

Liver disease

Hepatic HIF-1 α is upregulated following warm ischemia [27], and is required for restoration of gluconeogenesis in the regenerating liver [52], implying yet another potential use for PHD inhibitors in acute liver disease.

Peripheral vascular disease

In a model of limb ischemia in mice, PHD inhibitors enhanced HIF expression and downstream VEGF and VEGF-receptor Flk-1, leading to improved capillary density, indicating a potential therapeutic use of PHD inhibitors in promoting angiogenesis in ischemic diseases, such as severe peripheral vascular disease [54]. Transfection with HIF-1 α , combined with PHD inhibitor-treated bone marrow-derived angiogenic cells increased perfusion, motor function, and limb salvage in old mice with ischemic hind limbs [55]. Results of a phase-1 study in patients with critical limb ischemia indicate that transfection with a constitutively active form of HIF-1 α might also promote limb salvage [10]. Further clinical

trials with PHD inhibitors are currently under way in burn wound healing and salvage of critically ischemic limbs.

Oxidative stress

Enhanced cellular ROS concentrations, as happens with shock and tissue hypoxia, result in increased PHD activity, and this effect is antagonized by ROS scavengers [15]. This situation may lead to HIF de-stabilization and inadequate HIF response to hypoxia. For example, hypoxia-mediated HIF expression in the diabetic renal medulla is substantially improved by the administration of the membrane-permeable superoxide dismutase mimetic tempol [30]. It is, therefore, tempting to assume that ROS scavengers, as well as PHD inhibitors may improve tissue adaptive responses to hypoxia, coupled with oxidative stress. However, contradicting evidence exists, indicating that ROS might trigger HIF in the absence of hypoxia. This has been suggested by studying liver tissue in acetaminophen-induced liver injury, before the development of overt liver injury and hypoxia [56], and in aged well-fed animals [57]. The role of HIF stimulation during oxidative stress therefore needs further assessment.

Important considerations

HIF stimulation is not all-protective. The wide range of HIF-dependent genes, and its tight cross-communication with other key regulators of gene expression [13,58,59] raise concern regarding concomitant non-selective activation of protective as well as harmful systems. Among potential unwanted outcomes is the enhancement of tumor growth [60], promotion of fibrosis [61] or the induction of pre-eclampsia in pregnant women [62]. Indeed, whereas HIF activation is considered renoprotective in acute kidney injury, it may play a role in the progression of chronic kidney disease and certainly is an important factor in the promotion of renal malignancy [3,20].

Diverse characteristics and distribution patterns of different PHDs [5–7] and particular actions of various PHD inhibitors [11,37] might enable selective manipulation of the HIF system in a more desired way, selectively favoring advantageous HIF-dependent responses in preferred tissues. Furthermore, it is believed that activation of adverse responses requires protracted HIF stimulation, whereas short-term and transient HIF activation might suffice to activate tissue-protective systems without continuing induction of harmful systems. However, this concept needs confirmation in clinical trials.

Conclusion

Elucidating the mechanisms involved in HIF-mediated cellular responses to acute hypoxic stress has led to the

discovery of novel potential therapeutic options for the prevention or attenuation of tissue injury. The non-selective enhancement of gene expression by current modes of HIF augmentation warrants caution, since undesired enhancement of certain genes may be hazardous.

We anticipate that in the coming years the use of PHD inhibitors and other stimulants of the HIF system will be tested in many clinical scenarios associated with critical care and emergency medicine, while HIF silencing strategies may be tested in chronic diseases, such as malignancies and disorders with enhanced tissue scarring.

Acknowledgement

This report was supported by the Israel Science Foundation (Grant No. 1473/08) and the Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, Boston, MA.

Competing interests

The authors declare that they have no competing interests.

List of abbreviations used

EPO: erythropoietin; FIH: factor inhibiting HIF; HIF: hypoxia-inducible factors; HO: heme-oxygenase; HRE: hypoxia response elements; HSP: heat-shock proteins; PHD: prolyl-4-hydroxylase domain enzymes; ROS: reactive oxygen species; SUMO: small ubiquitin-like modifiers; VEGF: vascular endothelial growth factor; VHL: Von-Hippel-Lindau protein.

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Published: 22 March 2011

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doi:10.1186/cc9991

Cite this article as: Heyman SN, *et al.*: Hypoxia-inducible factors and the prevention of acute organ injury. *Critical Care* 2011, **15**:209.