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Xenon Misuse in Sports – Increase of Hypoxia-Inducible Factors and Erythropoietin, or Nothing but „Hot Air“?

Xenon Missbrauch im Sport – Vermehrung von Hypoxie induzierbaren Faktoren und Erythropoietin oder nur „heiße Luft“?

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SUMMARY

Experimental evidence suggests that xenon (Xe) is not completely inert but can affect the functional properties of proteins, particularly that of ion channels and of enzymes. According to recent reports xenon can activate the hypoxia-inducible transcription factors (HIF). A number of preclinical investigations (cell culture experiments, animal studies) has been performed concerning this, but the results have been volatile and the mechanism of HIF activation differed from that of hypoxia. Exposure to xenon (generally at 70 vol%) increased HIF-1α mRNA and HIF-1α protein levels in some studies, while in others, the HIF-2α mRNA and HIF-2α protein levels were increased instead. There is one single study in mice where increased renal levels of the HIF target proteins erythropoietin (EPO) and vascular endothelial growth factor (VEGF) were detected on Western blots at 24 h after xenon exposure of the animals. Effects of xenon treatment on the blood level of EPO have never been reported. No human data are available with respect to the HIF system and the production of EPO. Still, for reasons of precaution xenon has been included as HIF activator in WADA´s Prohibited List 2014. However, compared to the numerous chemical substances that increase HIF-dependent EPO synthesis in humans, the author considers the potential misuse of xenon in sports a minor issue.

Key Words: Blood doping, erythropoietin, gene expression, hypoxia, oxygen transport

ZUSAMMENFASSUNG

Es gibt experimentelle Evidenz, dass Xenon (Xe) nicht völlig inert ist, sondern die Funktion von Proteinen beeinflussen kann, insbesondere die von Ionenkanälen und Enzymen. Kürzlich wurde berichtet, dass Xenon unter bestimmten Bedingungen die Hypoxie induzierbaren Transkriptionsfaktoren (HIF) aktiviert. In diesen Untersuchungen wurden verschiedene präklinische Modelle genutzt (Zellkulturen, Versuchstiere), aber die Ergebnisse waren uneinheitlich und das HIF-Verhalten anders als bei Hypoxie. Die Begasung mit Xenon (in der Regel 70 Volumenprozent) führte in einigen Studien zur Anreicherung von HIF-1α mRNA und HIF-1α Protein, während dies in anderen nicht der Fall war, wobei die intrazellulären Spiegel von HIF-2α mRNA und HIF-2α Protein zunahmen. Es gibt eine einzige Untersuchung, und zwar an Mäusen, in der mittels Westernblot in Nierenextrakten 24 h nach einer Xenon-Behandlung eine Zunahme der HIF-Zielproteine Erythropoietin (EPO) und vaskulärer endothelialer Wachstumsfaktor (VEGF) nachgewiesen wurde. Einflüsse von Xenon auf die Konzentration von EPO im Blut sind nicht beschrieben. Es gibt keine Daten zu Xenon-Effekten auf das HIF-System und die EPO-Produktion beim Menschen. Dennoch ist Xenon vorsorglich als HIF-Aktivator in die WADA-Verbotsliste 2014 aufgenommen worden. Nach Meinung des Autors stellt der potentielle Missbrauch von Xenon – im Vergleich zu dem der zahlreichen chemischen Substanzen, welche bekanntermaßen die HIF-abhängige EPO-Synthese aktivieren – im Sport ein kleineres Problem dar.

Schlüsselwörter: Blutdoping, Erythropoietin, Genexpression, Hypoxie, Sauerstofftransport

INTRODUCTION

The academic sports scene was startled up in February 2014 by an article in "The Economist", reporting that xenon would be capable of artificially raising levels of erythropoietin (EPO) and therefore the production of red blood cells. It was further claimed that the gas was likely used in past Olympics, particularly by Russian athletes (1). The alleged mechanism of the action of xenon was by increasing cellular levels of the hypoxia-inducible factor (HIF), known to stimulate the production of EPO. The present article summarizes findings of the effects of xenon on the HIF transcription factors, as well as on their target genes and proteins, primarily EPO.

BIOLOGIC ACTIONS OF XENON FOCUSSING ON BRAIN

Xenon is a color- and odorless rare noble gas. Although generally considered inert, xenon may undergo distinct chemical reactions and exert biological effects. A telling example is the use of xenon as an anesthetic in medicine. In addition, xenon is thought to exert

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tissue-protective effects (6,18). Most commonly xenon was administered at 70 vol% in experimental studies.

In cell cultures and animal models, xenon was found to interfere with various proteins, including membrane receptors, pumps and ion channels. For instance, one may consider effects of xenon on neuronal cells. Xenon was shown to act as high-affinity glycine site N-methyl-D-aspartate (NMDA) receptor antagonist in mouse brain slices (3). Xenon dose-dependently suppressed NMDA-induced c-Fos expression in a rat model of brain injury (20). David et al. (7) have shown neuroprotective effects of xenon when administered up to 4 h after intrastriatal NMDA injection and up to at least 2 h after induction of transient brain ischemia in rats. In contrast to other anaesthetics (nitrous oxide and ketamine), xenon appeared to mediate neuroprotection via NMDA-antagonism without coexisting neurotoxicity (20). In vitro, xenon proved to inhibit other ligand-gated ion channels, such as nicotinic acetylcholine $\alpha_4ß_2$ receptors (27) and serotonin 5-HT3A receptors (25). Xenon was also reported to inhibit synaptic plasma membrane Ca^{2+}-ATPase (9). Furthermore, xenon has been shown to activate the 2-pore-domain K^+-channel TREK-1 that plays a role in neuroprotection (11).

Liu et al. (18) have recently summarized other biological effects and possible mechanisms of the asserted effects of xenon preconditioning in various organs. While a large number of preclinical studies have assigned positive effects to xenon, little support for its tissue-protective potential has been provided in human trials. Höcker et al. (14) performed a randomized, double-blinded controlled study to assess postoperative cognitive dysfunction (POCD) after xenon anesthesia in comparison to propofol. The study included 101 patients (65-83 yr) undergoing major abdominal or urologic surgery. The results show that xenon-based anesthesia was not associated with a decreased incidence of POCD in comparison to the control anesthesia with propofol (14).

FUNCTION OF HYPOXIA-INDUCIBLE TRANSCRIPTION FACTORS (HIF)

Cells are permanently threatened by hypoxia, meaning the situation when the rate of O_2-supply limits the rate of O_2-consumption. Hypoxia causes cellular dysfunction and eventually cell death. To prevent this, the activation of genes encoding adaptive proteins is of crucial importance. Some of these proteins act systemically, such as EPO that increases the O_2-capacity of the blood, while others act locally, such as vascular endothelial growth factor (VEGF) that promotes angiogenesis. At the single cell level the expression of glucose transporters and of glycolytic enzymes is enhanced on hypoxic stress (Fig.1). The genes for all of these proteins are under the control of the so-called hypoxia-inducible factors (HIF). HIF are heterodimeric transcriptional complexes (HIF-α/HIF-1ß). More than 1,000 HIF target genes have been identified, so far (24).

There are at least three different HIF-α subunits whereby HIF-1α and HIF-2α are the best characterized today. HIF-1α is more ubiquitously expressed, with HIF-1 playing major roles in metabolic processes, such as glucose metabolism (24). HIF-2α is more restricted to specific cell types, including endothelial cells and EPO-producing renal fibroblasts. Indeed, HIF-2 exerts delicate functions in angiogenesis and erythropoiesis (12). The HIF-α subunits possess two central oxygen-dependent degradation domains (ODDD) and two transactivation domains (TAD).

Both HIF-α and HIF-1ß are constantly translated in tissues. Nevertheless, HIF-α is usually missing in normoxic cells. That is so because distinct prolyl-residues in the ODDD of the HIF-α molecules are hydroxylated (Pro^{402} and Pro^{564} in HIF-1α, and Pro^{405} and Pro^{531} in HIF-2α) in an O_2-pressure dependent manner. This hydroxylation of HIF-α is catalyzed by specific prolyl-4-hydroxylase domain proteins (PHD-1, -2 and -3). The catalytic reaction requires α-ketoglutarate and is Fe^{2+}-dependent (for a review, see (21)). On prolyl-hydroxylation, HIF-α is immediately captured by the von Hippel-Lindau-tumor-suppressor protein (pVHL) and degraded by the 26S-proteasome. Furthermore, HIF-α is asparaginyl-hydroxylated (Asn^{803} in HIF-1α, and Asn^{847} in HIF-2α) in the C-terminal TAD in the presence of O_2. As a result of this hydroxylation binding of the transcriptional coactivator p300-CBP (CREB-binding protein) to the HIF complexes is prevented.

Because α-ketoglutarate and Fe^{2+} are required for HIF-α prolyl- and asparaginyl-hydroxylation, α-ketoglutarate competitors and Fe^{2+} chelators can inhibit the degradation and inactivation of the HIF-α proteins. Such chemicals enable HIF-α to enter the nucleus, to combine with HIF-1ß and to promote the transcription of HIF-dependent genes, even under normoxic conditions.

EFFECTS OF XENON ON THE HIF SYSTEM

Ma et al. (19) were the first to report that xenon affects HIF-1 dependent processes. Increased HIF-1α levels were detected in cultures of the human kidney proximal tubular cell line HK2 8 h after the cells were maintained in an atmosphere of 70% xenon and 30% O_2 for 2 h (19). Subsequent studies with HK2 cells showed that exposure to xenon enhances the levels of insulin-like growth factor-1 (IGF-1) and its receptor (28). When the effect of xenon in HK2 cells was compared to that of other noble gases including helium, neon, argon and krypton, xenon alone proved to increase HIF-1α and other signaling proteins, such as phospho-akt and Bcl-2 (22). Importantly, xenon produced similar increases in HIF-1α levels in cells of the renal carcinoma line RCC4, which presents with high levels of HIF-1α due to the lack of *VHL*, and in RCC4 cells stably transfected with *VHL* cDNA (19). These findings have led to the concept that xenon does not activate HIF via the canonical HIF-α destruction pathway.

In addition, the effects of xenon were studied in mice who inhaled 70% xenon and 30% O_2 for 2 h (19). The animals' kidneys were extirpated for quantitative real-time reverse transcription-PCR (rt-PCR) of HIF-1α mRNA and EPO mRNA, and for Western blotting of the protein levels of HIF-1α, EPO and VEGF. The results show that the renal HIF-1α mRNA levels were not increased on xenon exposure (19). Because the concurrent administration of rapamycin, the inhibitor of mTOR (mechanistic target of rapamycin), attenuated xenon-induced HIF-1α accumulation in the mice as well as in vitro (19,28), it has been proposed that xenon increases the translation of HIF-1α rather than preventing its degradation (28). HIF-1α protein levels were increased in renal samples from 2 h after the end of xenon exposure, with further elevation at 24 h. In contrast to this temporal pattern, renal HIF-1α accumulated in response to hypoxia (8 vol% O_2 for 3 h) declined rapidly to baseline levels within 2 h after the termination of hypoxia (19). Thus, the kinetics of the effects of xenon and hypoxia seem to differ. The renal protein levels of EPO and VEGF were moderately elevated at 24 h after xenon exposure (EPO by 160% and VEGF by 110%). When HIF-1α small interfering

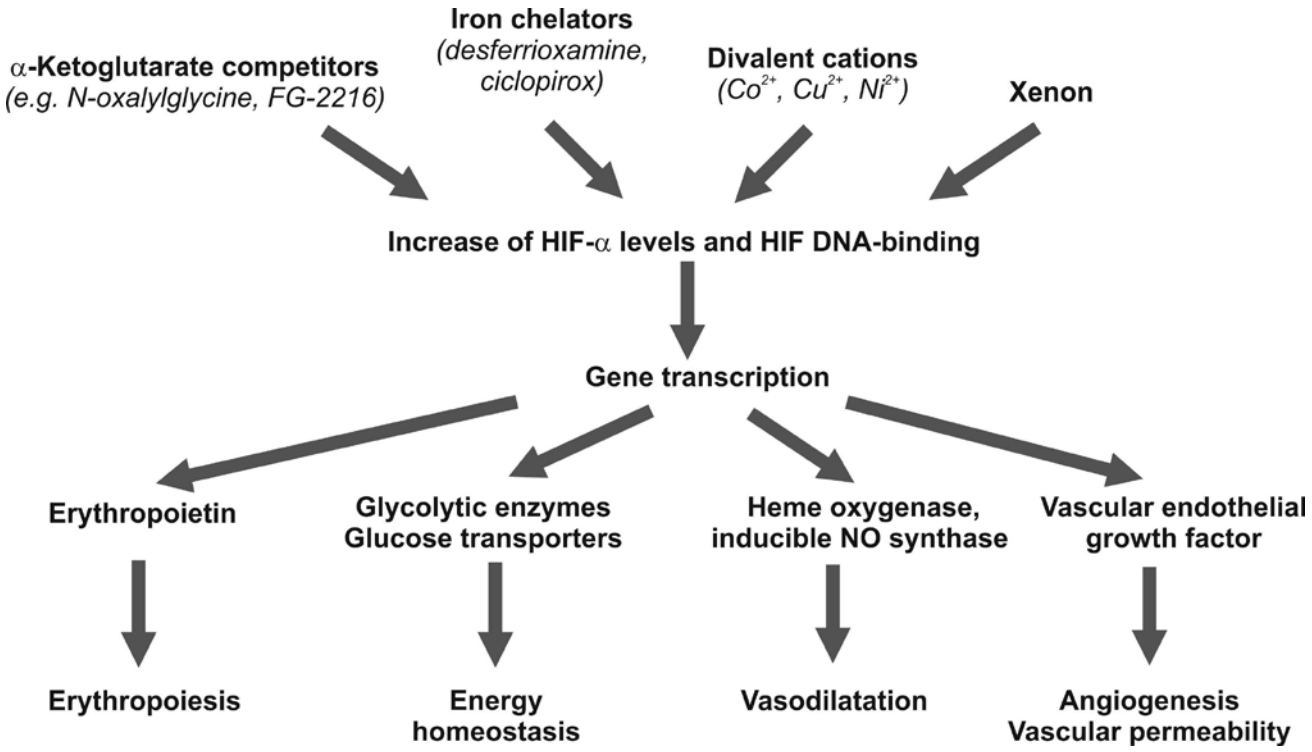

Figure 1: Pharmacological activation of the hypoxia-inducible transcription factors (HIF) and functional consequences. α-Ketoglutarate competitors, iron chelators and divalent cations inhibit hydroxylation and degradation of HIF-α („HIF stabilizers"). In contrast, evidence suggests that xenon stimulates HIF-α translation. More than 1,000 HIF target genes have been identified, involving erythropoiesis, glucose metabolism and blood vessels.

RNA (siRNA) was administered intravenously in order to knockdown the HIF-1α gene in the mice, HIF-1α siRNA duplexes were detected in kidney tubular cells 24 h after the injection. Reportedly, the administration of HIF-1α siRNA did not only reduce HIF-1α mRNA but also EPO mRNA levels (19). However, it must be critically noted that these findings are not fully plausible. First, EPO is not normally expressed by tubular cells but by fibroblast-like interstitial cells (2). Second, rather than HIF-1, HIF-2 is the physiological transcription factor that induces EPO in kidneys (23; for a review, see (12)).

Zhao et al. (28) investigated the renal protective properties of xenon in rat models of ischemia-reperfusion injury. Xenon treatment before or after hypothermia-hypoxia was found to decrease apoptosis and inflammation after re-oxygenation (28). In the syngeneic Lewis-to-Lewis isograft and the Fisher-to-Lewis allograft rat models of kidney transplantation xenon exposure to donors before graft retrieval or to recipients after engraftment decreased the expression of pro-apoptotic and pro-inflammatory proteins and improved renal function (29). Xenon-induced cell survival or graft-functional recovery was abolished by the use of HIF-1α siRNA (29).

Other investigators failed to confirm the effect of xenon on renal HIF-1α levels. For example, in the study by Jia et al. (15) male Wistar rats were intermittently exposed to either 70% xenon or 70% N_2 balanced with 30% O_2 before and during nephrotoxic gentamicin administration for 7 days. Xenon pretreatment upregulated HIF-2α and VEGF mRNA and protein levels, while HIF-1α mRNA or protein levels were unaffected (15). With regard to the three HIF PHDs, xenon treatment caused an increase in the PHD-2 mRNA level, whereas it suppressed PHD-1 and had no influence on PHD-3. While the study has shown that xenon can provide renoprotection, it did not consider renal EPO production (15).

With respect to other organs, xenon-induced upregulation of HIF-1α and phospho-akt has been implicated in neuroprotection in mouse models of transient middle cerebral artery occlusion (17). Cardioprotective effects of xenon, isoflurane and levosimendan were investigated in primary cultures of neonatal rat cardiomyocytes (10). HIF-2α (but not HIF-1α) and VEGF mRNA levels were increased on xenon treatment (70%) for 1 h. The protein level of HIF-1α was increased both by xenon and by levosimendan (HIF-2α protein data were not provided). Xenon-preconditioned cells also presented with increased levels of VEGF protein (10).

In conclusion, xenon appears to affect the HIF system and may modulate HIF-dependent gene expression, but the understanding of the molecular mechanisms of its action and the role of the distinct HIF-α isoforms is still incomplete.

XENON AND HIF-DEPENDENT EPO EXPRESSION: PRACTICAL IMPLICATIONS

EPO mRNA is expressed in several organs with the kidneys being the main production site in adult humans (for reviews, see (5, 12)). The EPO enhancer is normally activated by HIF-2 in collaboration with other transcription factors. However, HIF-1 may induce EPO expression under experimental conditions.

Shortly after the World Anti-Doping Agency (WADA) was alerted to the substance xenon and its potential performance enhan-

cing characteristics the WADA List Committee approved the option to modify section S.2.1 of the 2014 Prohibited List, where HIF activators like xenon or argon have now been specifically identified. The amended 2014 Prohibited List has come into effect on September 1, 2014 (www.wada-ama.org). While the inclusion of xenon in the list of forbidden substances is an appropriate safety measure, the real threat by means of xenon in sports is likely of secondary importance, for the following reasons. (i) All of the speculations in the daily press are scientifically supported by one single publication in an international refereed journal (19). In that study HIF-1α, EPO and VEGF were demonstrated by Western blots of mouse kidney extracts. As noted above, most data on biological effects of xenon are from preclinical experimental studies, while the role in humans is still unclear, in general (13). (ii) There is no report (even no report from animal studies) describing effects of xenon on circulating EPO levels. Moreover, there are no published data showing that the inhalation of xenon is effective in stimulating red blood cell production thereby enhancing O_2 transport in humans or other organisms. (iii) Because of the high xenon concentrations needed and the enormous costs, xenon is clinically administered via special respirators that allow scavenging of exhaled xenon (6). (iv) Thevis et al. (26) have already provided a first study of how the abuse of xenon could be detected from doping control samples with the instrumentation commonly available in sports drug testing laboratories.

On the other hand, EPO production and red cell mass can be increased quite readily by exposure to low O_2 pressure (inspiring thin air at altitude, training or living in hypoxia chambers). Furthermore, there are a number of chemical substances (cobalt salt, synthetic α-ketoglutarate competitors and other HIF-stabilizers) which potently induce HIF-dependent EPO expression (Fig. 1). These compounds are clearly effective in humans. Cobalt salt is probably the most severe stimulator of EPO production (8), and first steps have been taken to measure the urinary concentration of cobalt for detection of its misuse by athletes (16). It is of utmost importance, indeed, to develop methods for the detection of small molecule HIF-stabilizers (4) and to inform sportsmen of the possible side effects associated with their intake.

To conclude, in this author´s mind xenon misuse in sports is a minor issue compared to the potential hazards by intake of any of the numerous chemical substances known to stimulate HIF-dependent EPO synthesis.

Conflict of interest

The author has no conflicts of interest.

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