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LETTER TO THE EDITOR

EPO and doping

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To the Editor,

It is with great interest that we read exchanges on intermittent hypoxic (Boning 2009; Ferretti 2009) exposure as a potential doping procedure. Erythropoietin (EPO) does introduce potential concerns in terms of doping, both due to its effects and side effects. An earlier publication on exogenous EPO (Noakes 2008) clearly showed an increase of sub-maximal performance with a significant increase of time to exhaustion after prolonged rHuEPO administration. It is clear that in healthy subjects, at sub-maximal effort levels, cardiac output is sufficient to maintain adequate oxygen delivery to active muscles. Accordingly, it appears that EPO achieves more than increasing blood oxygen carrying capacity alone. Being both a hormone and a cytokine, the actual actions of EPO are complex: EPO is neuroprotective and even neuroregenerative in both the peripheral and central nervous system. Moreover, EPO also has antiapoptotic effects that may be coupled to antioxidant activity.

Exercise-induced plasma volume contraction is linked to EPO production (Roberts et al. 2000), whereas the hormone itself appears to alter plasma volume as well. Any of these known actions of EPO could explain a possible increase in exercise capacity. The traditional view of EPO as a haemopoietic agent, therefore, needs to be expanded to incorporate these additional effects and studies on the effects of EPO should be designed in such a way that these may be considered more carefully.

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Urine testing for exogenous EPO has been available for several years. It has been used in international cycling events. However, this does not exclude the possibility of endogenous EPO induction. Intermittent hypoxia (Sanchis-Gomar et al. 2009) is the natural trigger for EPO production, and is widely used by (endurance) athletes since many years. We have recently described the use of intermittent hyperoxia to stimulate EPO production (Balestra et al. 2006). This has subsequently been shown to be capable of increasing haemoglobin levels in a chronically anaemic patient (Burk 2007).

The mechanism proposed to explain this "normobaric oxygen paradox" involves a complex play of oxygen-free radicals (OFRs) presence and their "scavenging" enzymes in the cell. In the presence of OFR, the continuously produced hypoxia-inducible factor alpha (HIF-1α) is instantly linked to the (tumour suppressing) Von Hippel Lindau Protein (VHLp). This complex is subsequently ubiquitinized in the prolyl-oxidase pathway and finally recycled in the proteasome. In a hypoxic state, the absence of OFR prevents HIF-1α from linking to VHLp, and allows it to be dimerized with the HIF-1β dimer. This hybrid HIF complex can then start a cascade of EPO gene expression and subsequently, de novo EPO synthesis. In a hyperoxic situation, the presence of OFR will trigger an upregulation of OFR scavenging systems; notably, the activity of the glutathione synthetase enzyme is increased, resulting in an increased availability of glutathione. When now the cell resumes its "normoxic" state, the increased glutathione will scavenge all OFRs present, "mimicking" a hypoxic situation, and allowing the HIF dimers to bind and start the EPO gene expression.

In our experience, this mechanism has allowed a clinically valuable increase in haemoglobin in patients with anaemia due to a variety of causes, including bone marrow

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impairment. Patients who breathed pure oxygen for 30°–45 min three or four times per week showed an increase in haemoglobin of about 7–10% after 10 days of treatment. Applying the same protocol to healthy subjects provides a similar effect although it does not achieve a 10% increase as for the anaemic patients.

In summary, hypoxia is not the only trigger for increasing EPO. Relatively short periods of oxygen breathing are likewise capable of producing this effect. Competitive breathhold diving has the greatest potential for increasing EPO levels. Yet, this does not achieve potential harmful levels of haemoglobin while affording the individuals with some neuroprotective effects. Accordingly, the rationale for inducing EPO through prior oxygen breathing for a limited period may be entirely appropriate (Balestra et al. 2006). It is interesting to note that elevated plasma EPO levels do not increase breathholding time. Therefore, this does not result in a doping effect.

Therefore, we thoroughly concur with Guido Ferretti who argues against considering intermittent hypoxia as a doping procedure. In addition, we would like to add that endogenous EPO may offer some antioxidant and neuroprotective benefits and should be considered as an injury-preventive agent.

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