EDITORIAL

Synthesis, function and possible new avenues for erythropoietin

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For decades the only function of erythropoietin (EPO) was thought to be the regulation of arterial oxygen content, and accordingly recombinant human EPO has been administrated to millions of anaemic patients since the late 1980s. Today EPO must be recognized as one of the most important and most profitable pharmacological agents worldwide. Despite its wide use in medicine, however, several fundamental discoveries within the synthesis and function of EPO have been made over the last few years. For example, although renal hypoxia is still considered the main trigger for the synthesis of EPO released from the kidneys, skin hypoxia was recently proposed also to be important for the erythropoietic response to hypoxia, and furthermore astrocytes may contribute up to 40% of systemic EPO concentrations. These are indeed provocative findings! The experiments were completed in a series of knock-out animals and whether these findings are also relevant for humans still needs to be elucidated but seems unlikely since EPO producing organs such as brain, liver, spleen and lung are not able to substitute for renal EPO in chronic kidney disease.

Due to the seemingly endless stream of articles published on the topic of non-erythropoietic functions of EPO, and findings such as the above mentioned animal knock-out experiments, *The Journal of Physiology* has published a set of three reviews on EPO whose purpose is to highlight the most promising and relevant results obtained from cell culture and animal studies and determine their relevance for human beings/clinical practice. For this purpose Wolfgang Jelkmann has written an review highlighting the present understanding of the control of EPO production. In this regard, besides the by now well documented involvement of the HIF complex in hypoxia induced EPO synthesis, also the ability of angiotensin II to promote EPO production in response to haemorrhage deserves further investigation (Jelkmann, 2011). At present the molecular basis for this is completely lacking. Johannes Vogel and Max Gassmann work with transgenic animals and report on exciting findings in their review based on such animals (Vogel & Gassmann, 2011). They highlight that EPO, independent of its erythropoietic function, is essential for development and, based among others on ischaemia–reperfusion models that EPO may become relevant in other clinical settings than in those applied today. Niels Olsen and I cover relevant findings based on human physiology studies (Lundby & Olsen, 2011). Of importance in this regard is that EPO may regulate oxygenation by decreasing plasma volume, and that EPO seems to induce hypertension besides by an enhanced blood viscosity by acting as a vasoconstrictor. Finally the promising effects of EPO on metabolism based on animal experiments are discussed in a human context.

As stated by Wolfgang Jelkmann a few years ago, EPO does seem younger than ever, and a collaborative and focused effort between molecular researchers, human physiologists and clinicians seems to be needed to unravel the basis for EPO in future healthcare besides those known today.

References

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