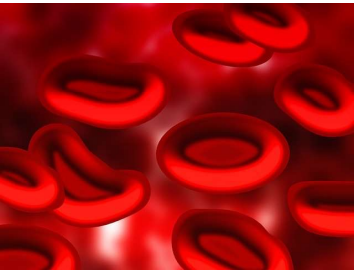
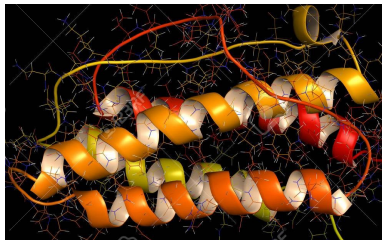
The secrets of Epo



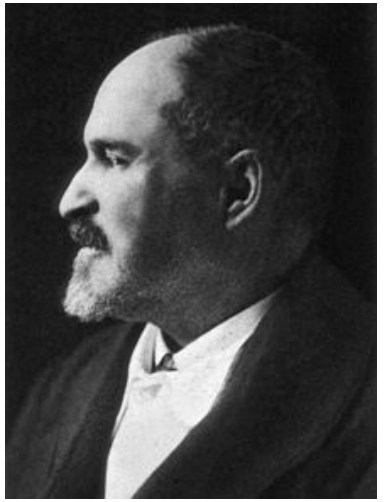


The hematopoetic and
non hematopoetic effects of Epo

Aurélien Pichon
@aurelien.pichon

Introduction

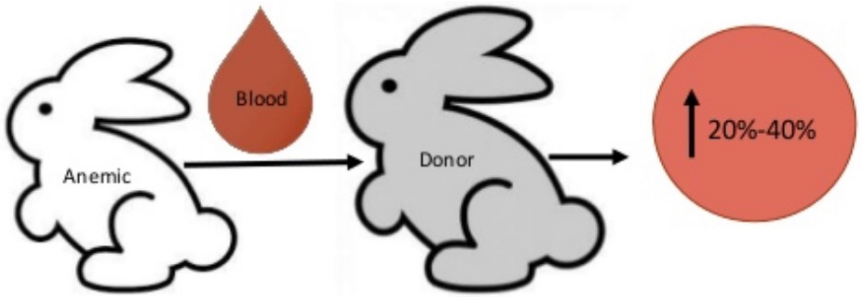
- **In 1890, Dr Viault observed after a travel in Morococha (Peru - 4200 m) from Lima an increase in red blood cell (RBC) number : from 5 to 7,1 millions / mm3:**



➔ **Hypothesis of a direct effect of a decrease in oxygen tension (hypoxia) on the RBC synthesis**

- **In 1906 Clotilde-Camille Deflandre and Paul Carnot discovered that an injection of serum from anemic rabbits to normal rabbits conduced to a large rise in RBC production:**

➔ **Hypothesis of a 'factor' in plasma that could regulate RBC production (erythropoiesis)**



Bunn F Cold Spring Harb Perspect Med. 2013

Introduction

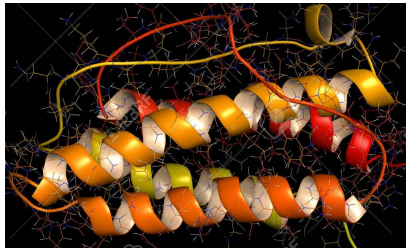
- **In the 50th, identification of Epo production in kidney and in liver**

➔ **Jacobson et al. in 1957 in rats and Nathan et al. in 1964 in human**

- **In 1977, Goldwasser and his team produce 8 mg of human purified Epo (Miyake et al. 1977)**
- **In 1985 the Epo gene was identified, cloned and proved to be expressed in mammals (Jacobs et al. 1985; Lin et al. 1985)**

➔**This allow the production of Epo in larger quantity**

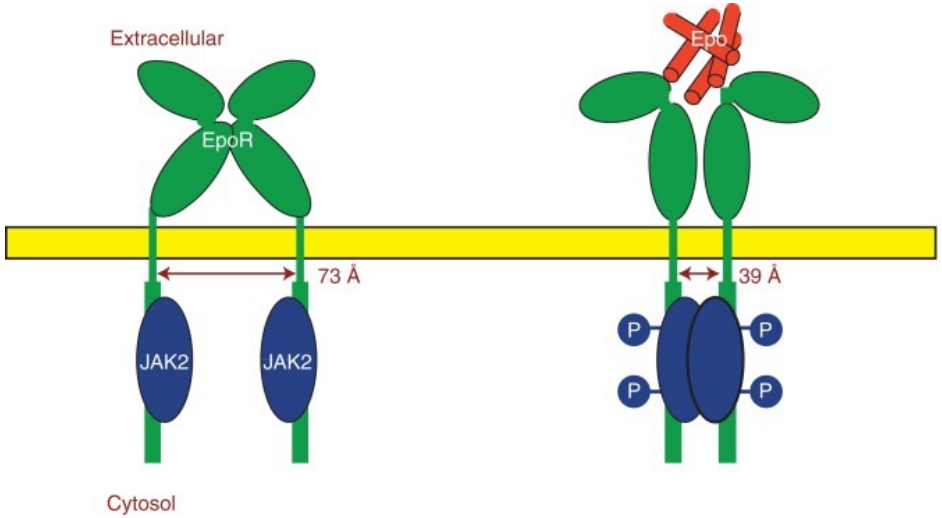
- **In 1989, the FDA allow the use of Epo to treat anemia**



Godwasser 1996 Perspect Biol Med

Introduction

- **Glycoprotein of 34 KDa**
- **Cytokine: role in cellular signalization**
- **Production: mainly kidney in adult and liver in the fetus**
- **Acts due to its binding to Epo receptor**
- **Transmembrane receptor (Epo-R) and soluble (sEpoR)**
- **The Epo/Epo-R ratio or Epo/sEpoR ratio could be of importance for the physiological effect of Epo**

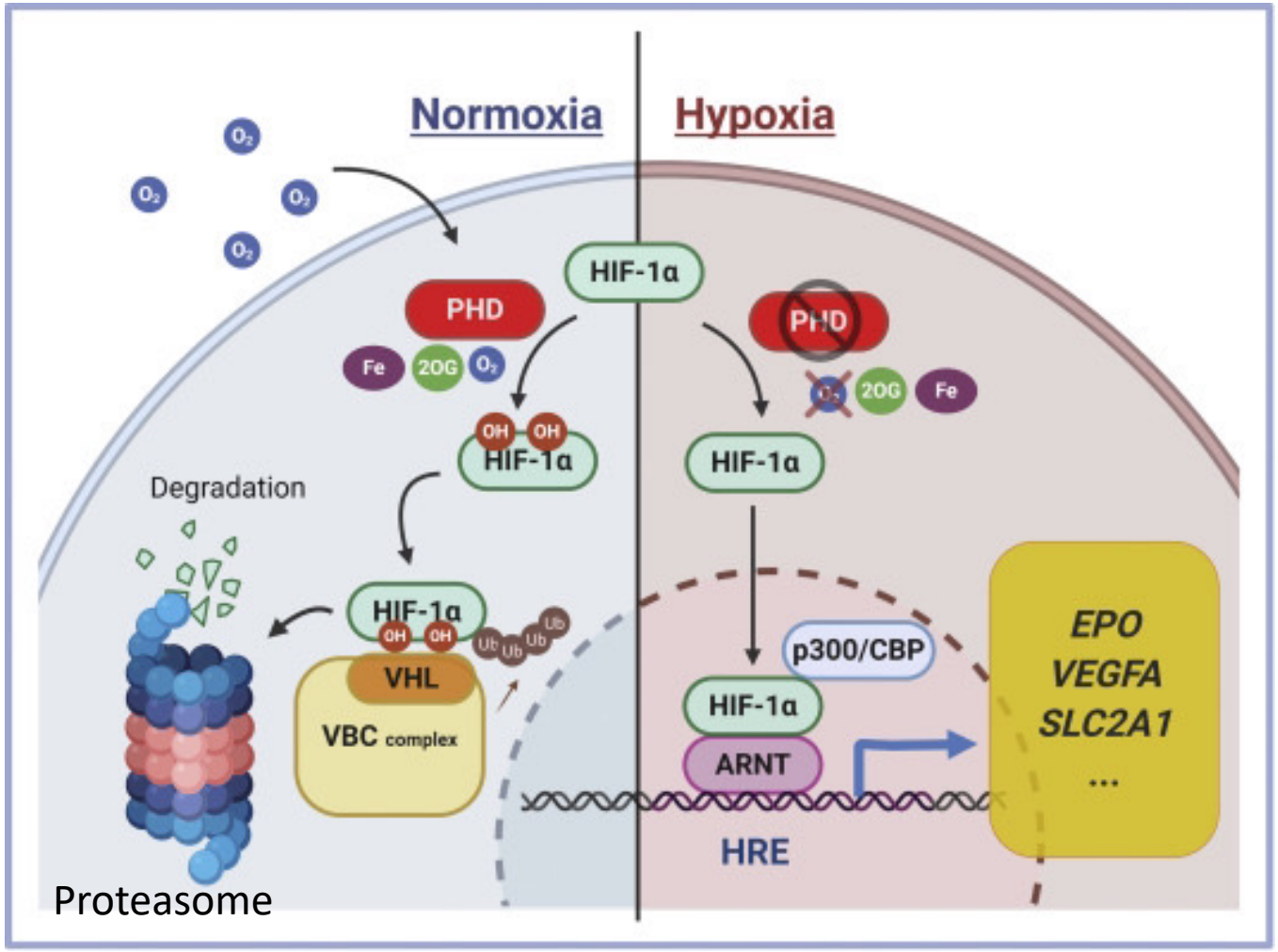


Bunn F Cold Spring Harb Perspect Med. 2013 ; Mulcahy 2011 Semin Oncol

Introduction

- **Epo synthesis is link to HIF pathway**
- **2019 Nobel Prize in Physiology or Medicine:**

William G. Kaelin Jr, Sir Peter J. Ratcliffe, and Gregg L. Semenza "for their discoveries of how cells sense and adapt to oxygen availability." and HIF regulations

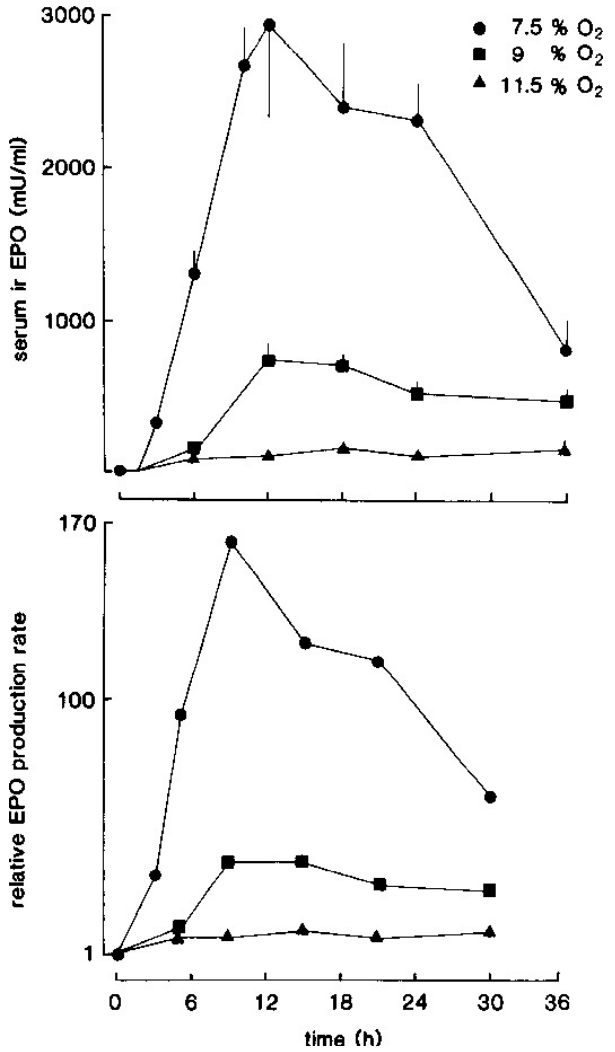


Oxygen-dependent regulation of hypoxia-inducible factors. Under normoxic condition (left panel), hypoxia-inducible factor (HIF)-1α is hydroxylated at proline residues (Pro402 and Pro564) by prolyl-hydroxylase enzymes (PHD). The hydroxylation is catalyzed by oxygen, iron, and α-ketoglutarate (also named 2-oxoglutarate, 2OG). The hydroxylated HIF-1α is recognized by von Hippel-Lindau (VHL), which is part of an E3 ubiquitin ligase complex, VHL-Elongin BC-CUL2 (VBC) complex. The VBC complex transfers ubiquitin and the ubiquitinated HIF-1α is transported to the proteasome for degradation. Under hypoxic condition (right panel), the enzymatic activity of PHD is decreased because of insufficient oxygen (O_2). The un-hydroxylated HIF-1α is not recognized by VHL, and remain un-ubiquitinated. The un-ubiquitinated HIF-1α translocates from cytoplasm into nucleus, and heterodimerizes with aryl hydrocarbon receptor nuclear translocator (ARNT). The HIF-1α/ARNT dimer binds hypoxic responsive element (HRE) DNA sequence and recruits p300/CBP to activate transcription of genes such as *EPO*, *VEGFA*, and *SLC2A1*. Factor inhibiting HIF (FIH)-1 inhibits transactivation activity of HIF-1α by hydroxylating its asparagine residue (Asn803) and interrupting the interaction between HIF-1α and p300/CBP. HIF-2α is regulated similarly as HIF-1α.

Pan et al. 2021

Introduction

- **Epo production is dependent of hypoxia severity**



Time-dependent change in serum irEP (top) and underlying alterations in relative EPO production rates (bottom) in rats exposed to 3 different degrees of normobaric hypoxia. Serum irEP values are means t SE for 5 animals each, except a 12-h value for 7.5% O2 (n = 13). Relative production rates were calculated from increase in serum EPO levels, assuming a constant EPO half-life of 110 min.

Eckardt et al. 1990

Introduction

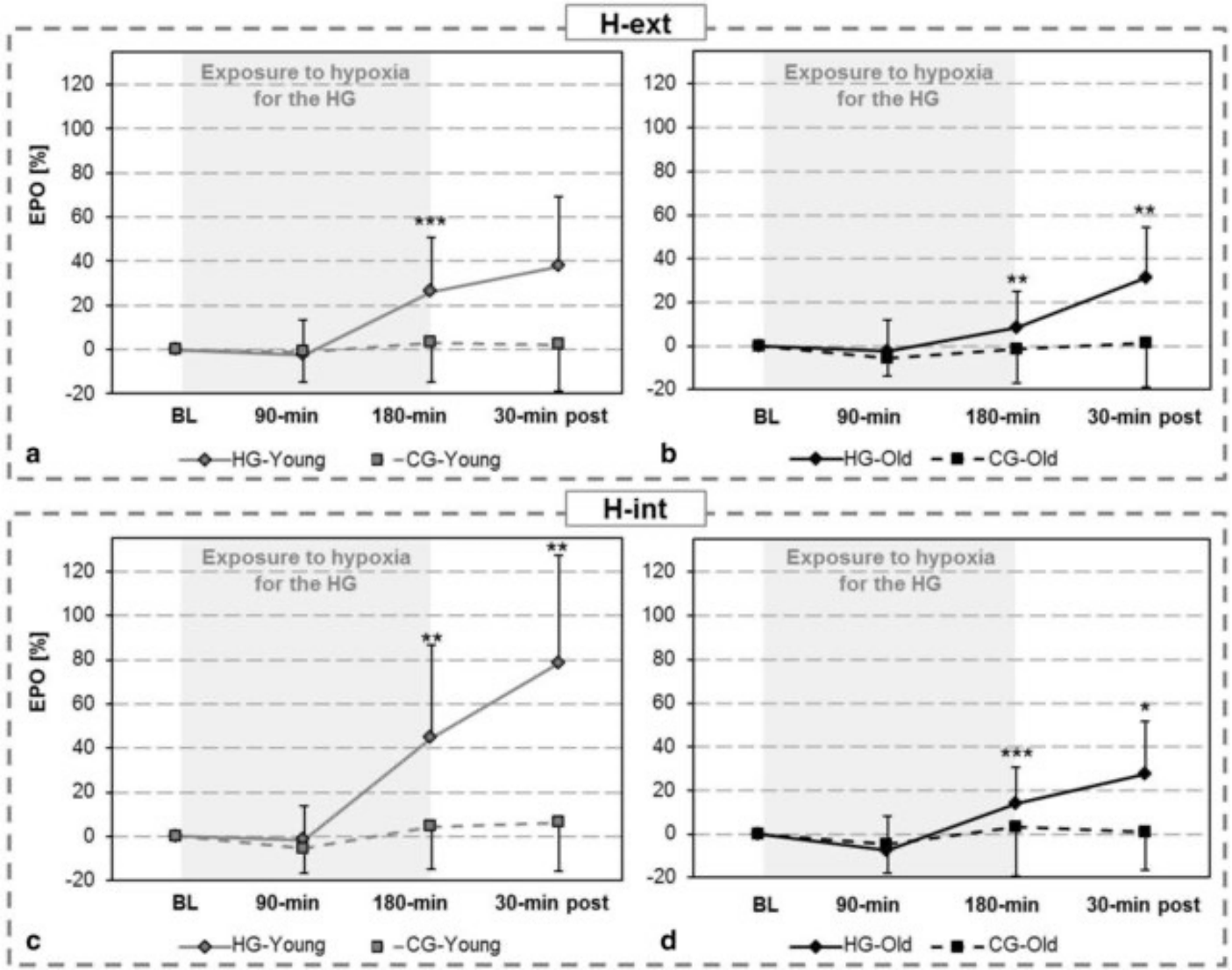
- **Even short term hypoxic exposure (3h) increase Epo level in young and old people**

Percentage change of serum EPO related to the baseline during a single normobaric hypoxic exposure over 3 h as well as 30 min after administration of hypoxia in young and old people. The intensity of hypoxia was either adjusted to a fraction of inspired oxygen (FiO2) of 13.5% (H-ext) for a young and b old people or to an oxygen saturation of the blood (SpO2) of 80% (H-int) for c young and d old people (time points for measurement EPO: baseline: BL; after 90 and 180 min of hypoxic exposure: 90 min, 180 min; 30 min after the exposure to hypoxia: 30-min post; HG hypoxia group, CG control group; time effects in relation to the previous time point: *p < 0.050, **p < 0.010, ***p < 0.001)

Torpel et al. 2019

13,5% O_2

80% SpO_2



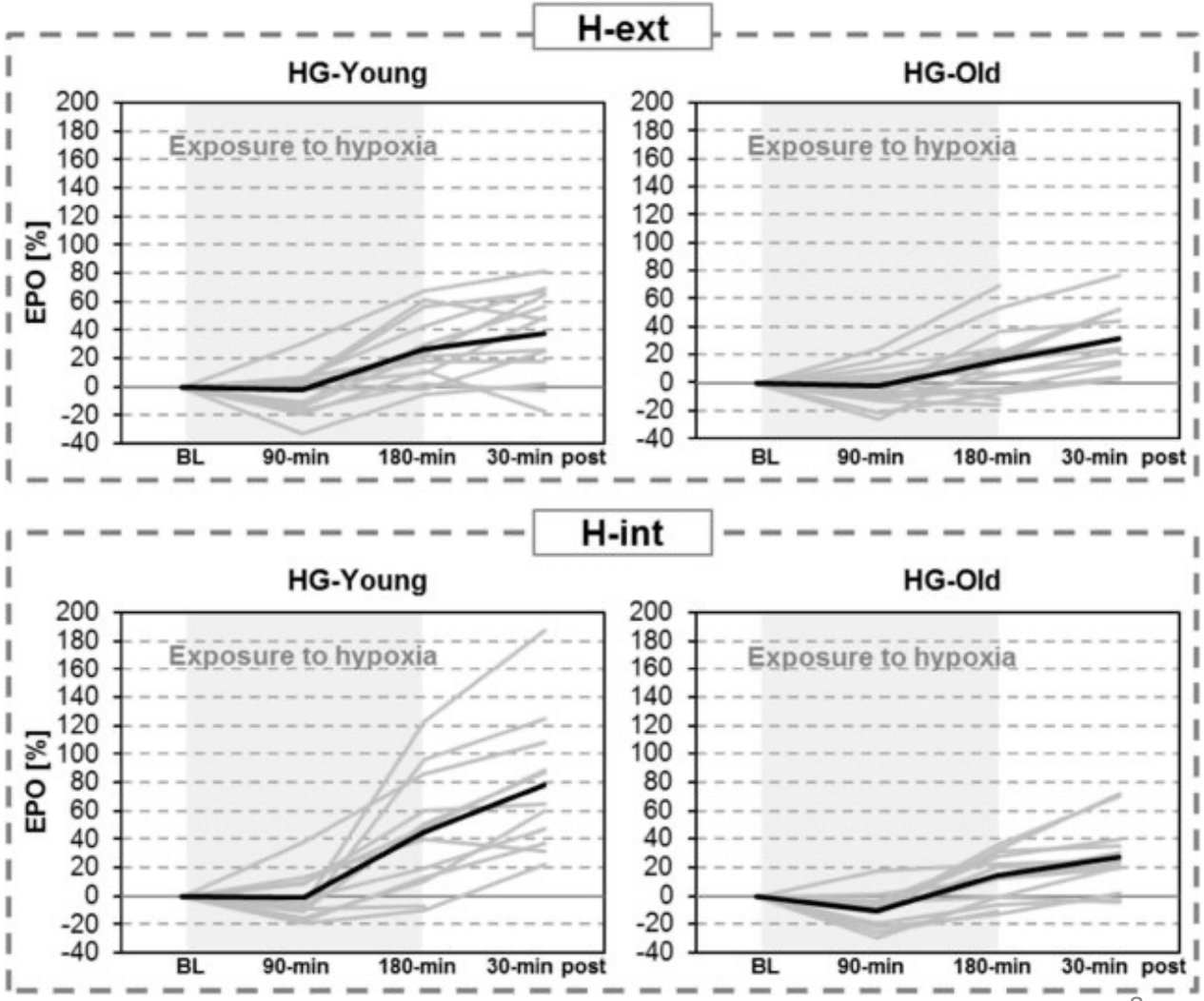
Introduction

- **High inter-individual heterogeneity of Epo production**

Inter-individual percentage change of serum EPO related to the baseline measurement during a single normobaric hypoxic exposure over 3 h as well as 30 min after administration of hypoxia in young and old people (the gray lines denote single participants, the black lines denote the mean value of the group). The severity of hypoxia was either adjusted to a fraction of inspired oxygen (FiO2) of 13.5% (H-ext) for young and old people or to an oxygen saturation of the blood (SpO2) of 80% (H-int) for young and old people (time points for measurement EPO: baseline: BL; after 90 and 180 min of hypoxic exposure: 90 min, 180 min; 30 min after the exposure to hypoxia: 30 min post; HG hypoxia group, CG control group)

13,5% O_2

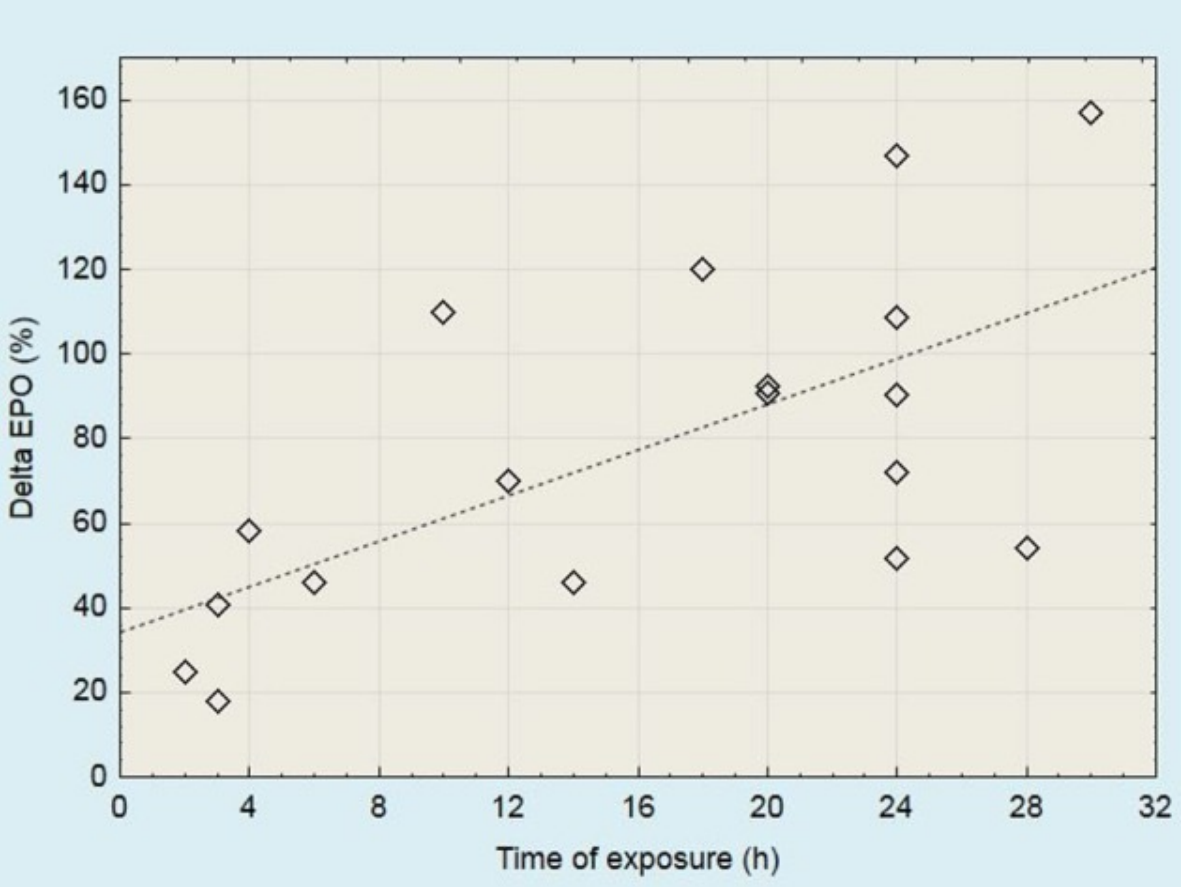
80% SpO_2



Torpel et al. 2019

Introduction

- **Epo secretion could be maximal in athletes 24h post hypoxic exposure**

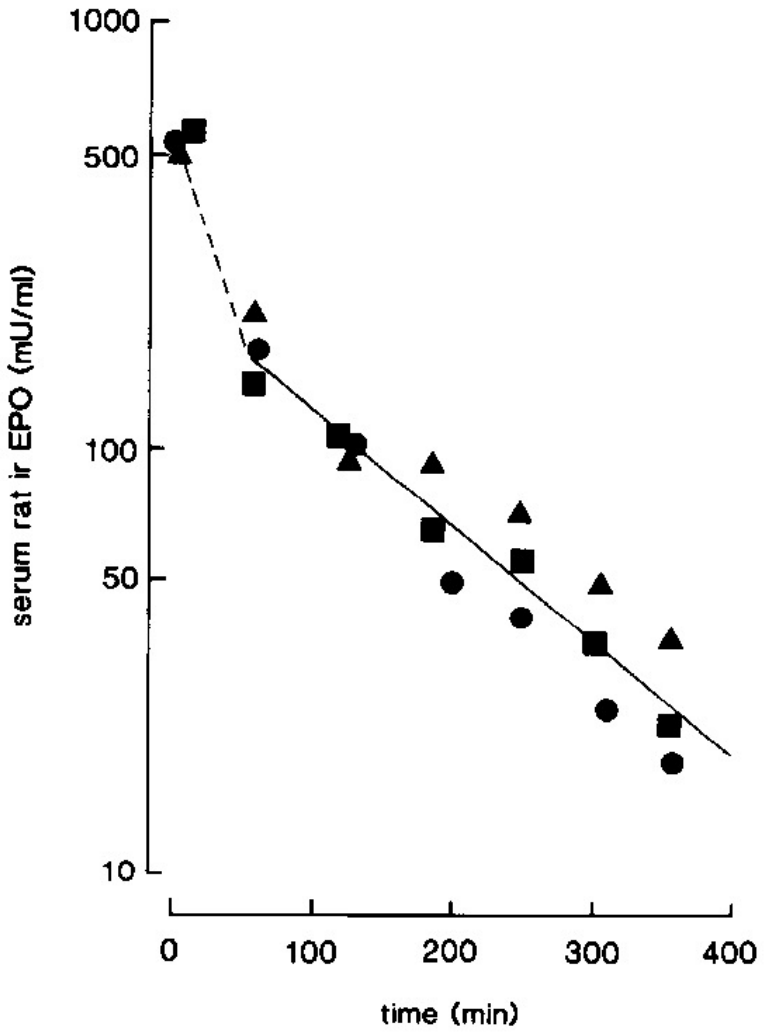


Acute changes in serum EPO levels following the exposure to moderate altitude (2,000 to 3,100 m). Data derived from studies published by Chapman et al. (1998, 2010, 2014); Stray-Gundersen et al. (2001); Jedlickova et al. (2003)*; Friedmann et al. (2005)*; González et al. (2006)*; Mounier et al. (2006); Wehrlin et al. (2006); Mackenzie et al. (2008); Clark et al. (2009)*; Neya et al. (2013); Badenhorst et al. (2014); Czuba et al. (2014). *More than one measuring point has been presented in these papers.

Płoszczyca et al. 2017

Introduction

- **Half life of exogenous Epo is short (<2 hours)**
- **Half life of endogenous Epo would be about 7/8 hours**

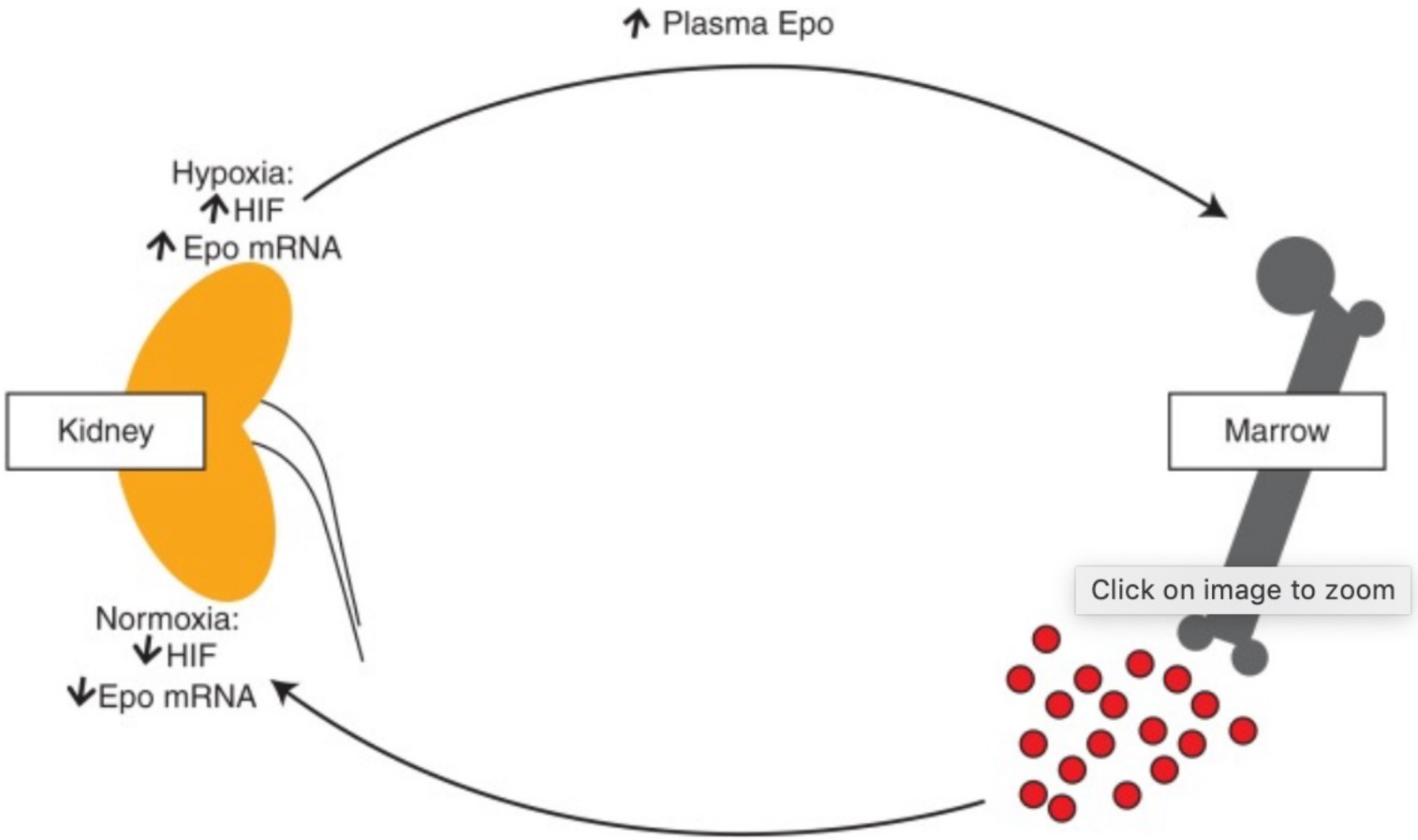


Serum clearance of irEP in 3 rats injected with homologous EPO at a concentration of 20 U/kg body wt. The individual basal value was subtracted from the serum value. After 1 h, values fitted a single exponential regression line: log serum irEP (mu/ml) = -0.0027 x time (min) + 2.36, r = -0.94. The resulting tl/, is 110 min

Eckardt et al. 1990

Erythropoiesis

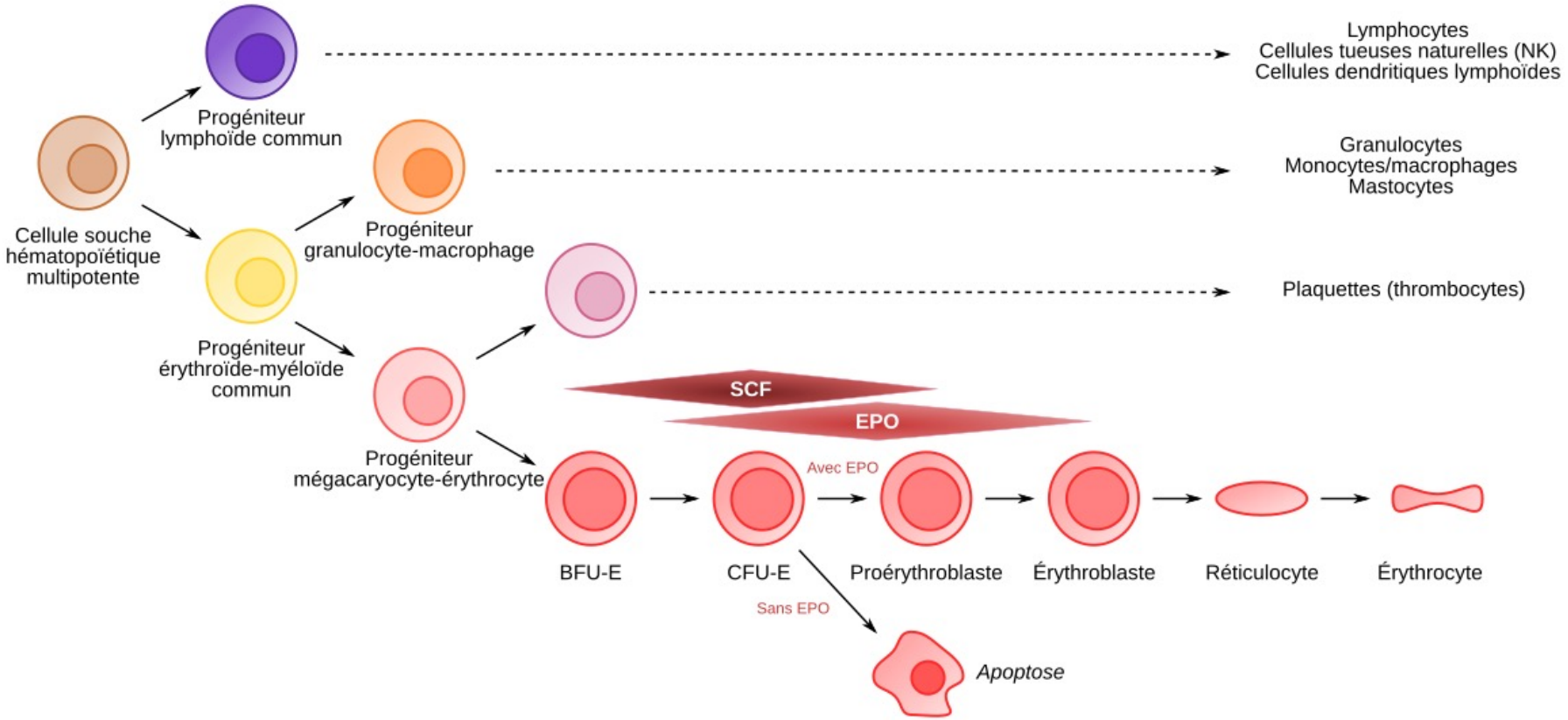
- **Major role of Epoi on erythropoiesis and in the homeostasis regulation**



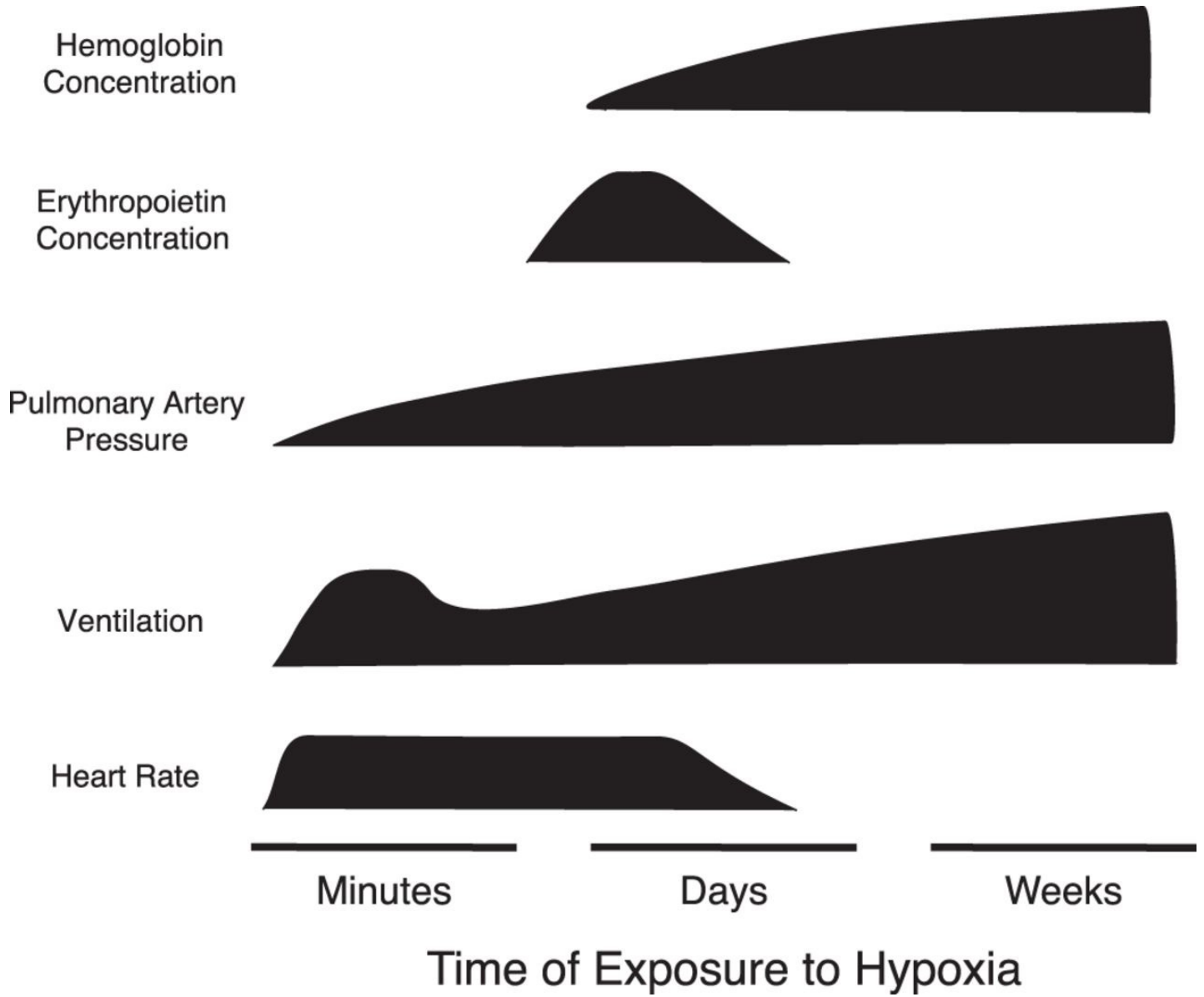
Bunn F Cold Spring Harb Perspect Med. 2013

Erythropoiesis

- **Has a major role (unique?) in erythropoiesis**
- **Presence of Epo-R on erythroid progenitors and Epo promotes survival, proliferation and differentiation of progenitor erythroid cells**



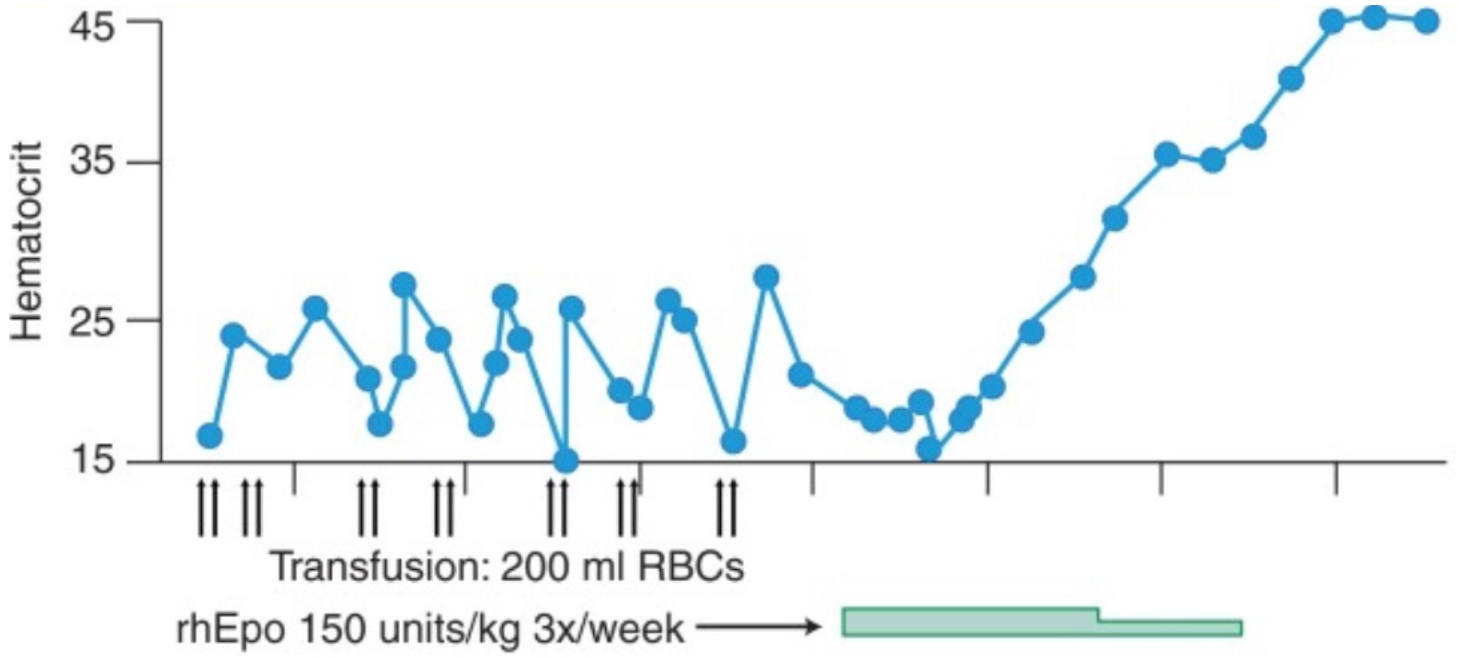
Erythropoiesis



Luks et al. 2015

Erythropoiesis

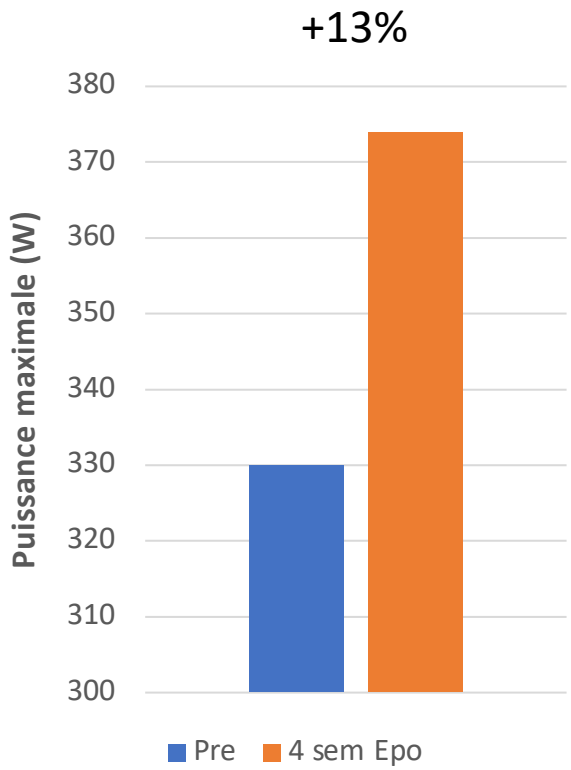
- **Efficiency of exogenous Epo shown in vivo to treat anemia**

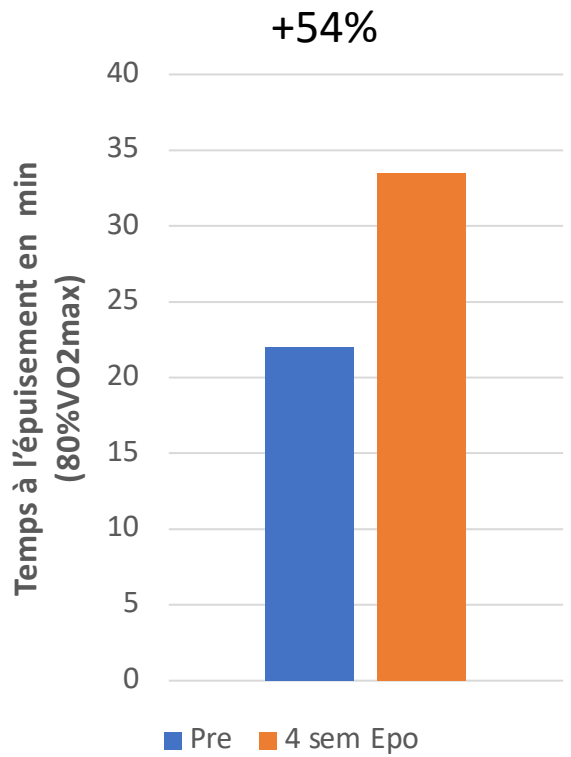


Eschbach et al. 1987

Erythropoiesis

- **Efficiency of exogenous Epo identified to increase performance…**





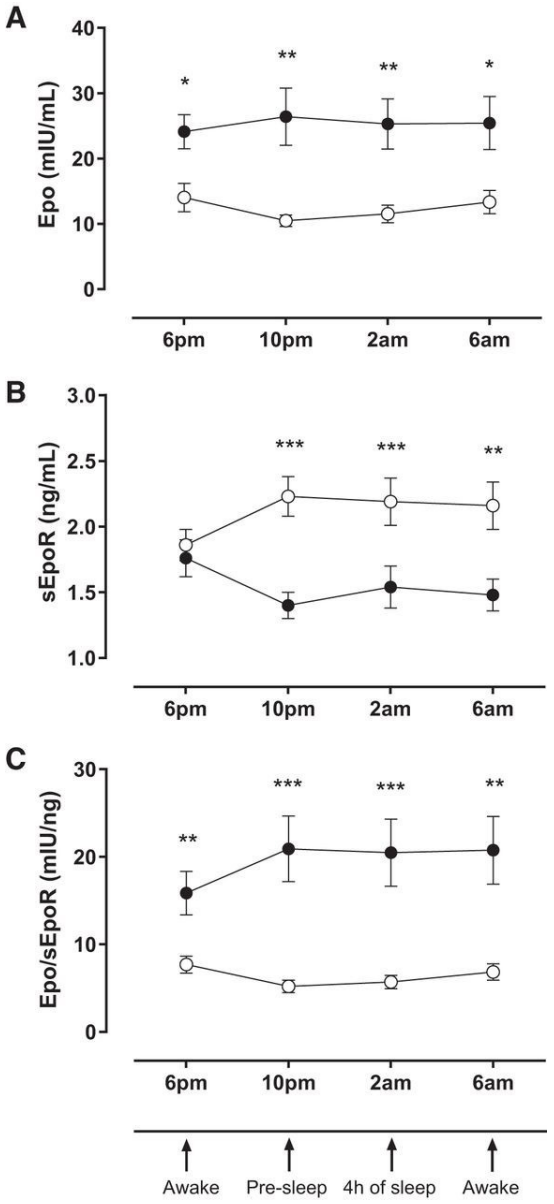
Thomsen et al. 2007 ; Heuberger et al. 2017

Erythropoiesis - CMS

- **Epo concentration was higher in Chronic Mountain sickness patients**
- **sEpoR expression was lower in CMS patients**

→ Amplify the binding of Epo to EpoR and consecutive increase in erythropoiesis?

Nahri et al. 1997



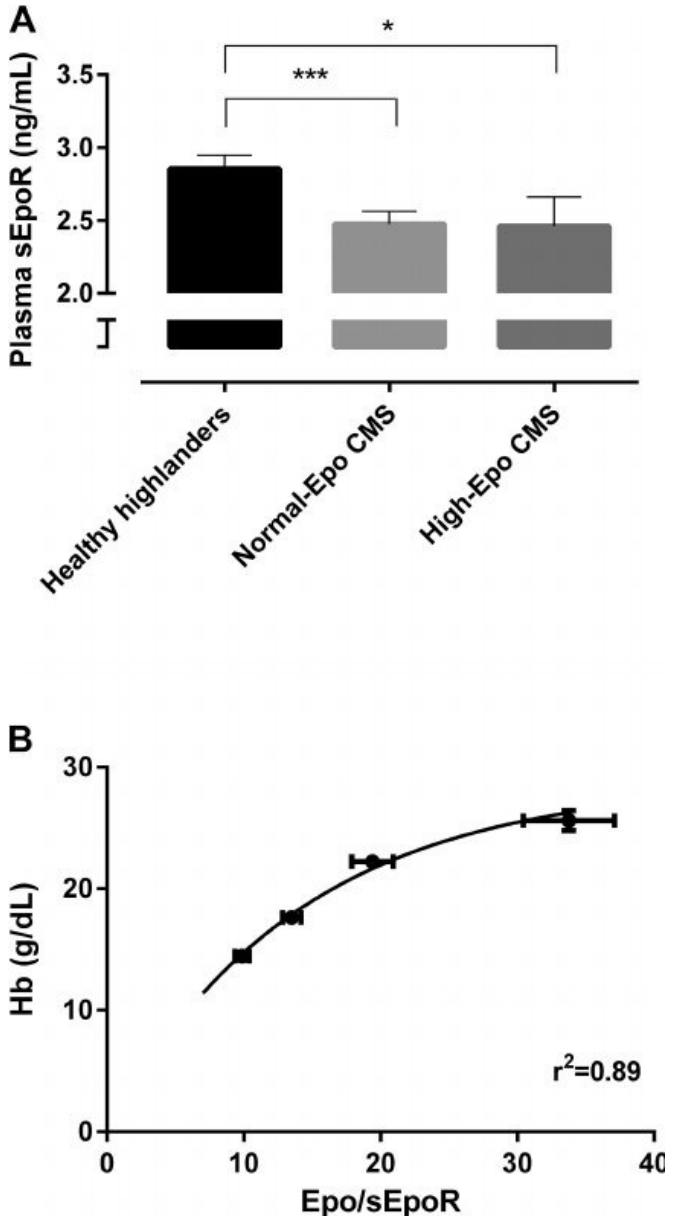
Time course of erythropoietin (Epo), serum soluble Epo receptor (sEpoR), and the Epo-to-sEpoR (Epo/sEpoR) ratio in patients with Chronic Mountain Sickness (●, n = 23) and healthy highlanders (○, n = 16). The figure shows Epo (A) and sEpoR (B) concentrations and the Epo/sEpoR ratio (C) of each group at every time point. Arrows on parallel x-axis each point at specific time points on Epo, sEpoR, and Epo/sEpoR measurements and corresponding time points at 10 PM (presleep) and 2 AM (4 h of sleep) from Fig. 1. Values are expressed as means ± SE. *P < 0.05, **P < 0.01, ***P < 0.001.

Villafuerte et al. JAP 2016

Erythropoiesis - CMS

- **Epo/sEpoR ratio higher in CMS patients**
- **The Epo/sEpo-R ratio seems to be important for the erythropoiesis response in CMS patients**

→ **increase sensitivity to Epo**
→ **increase Epo availability**
→ **worsen CMS ?**

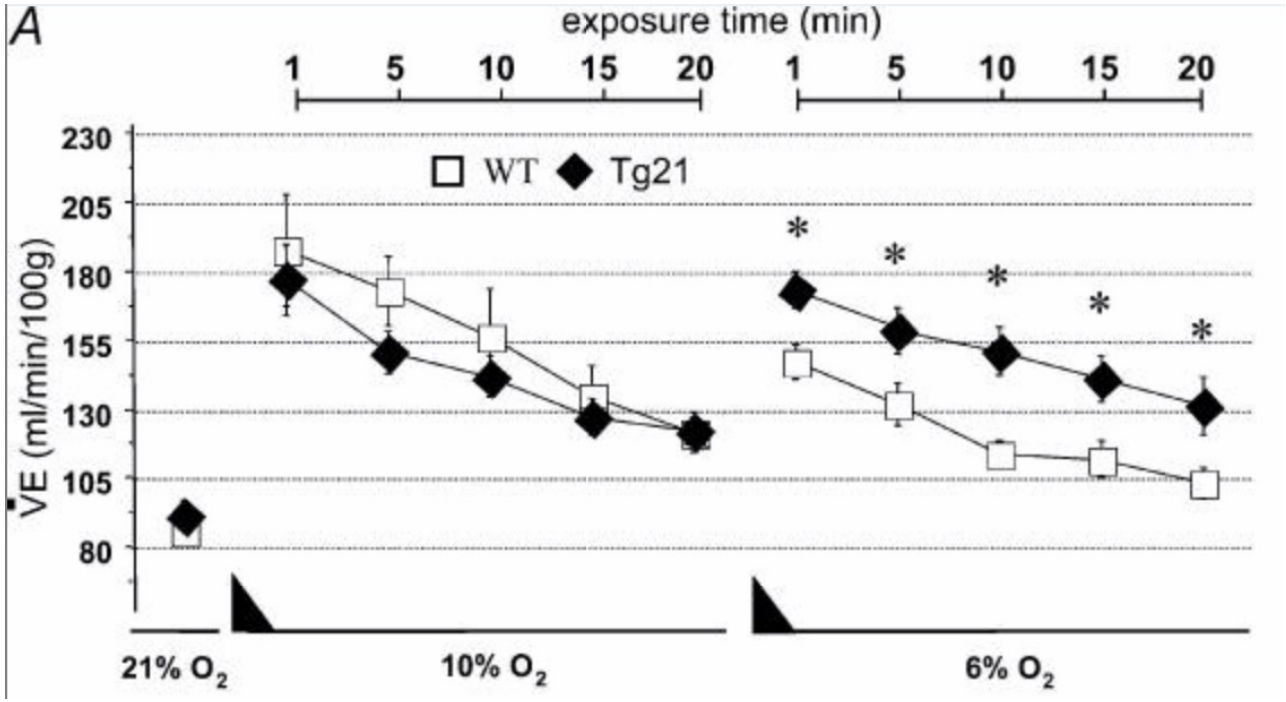


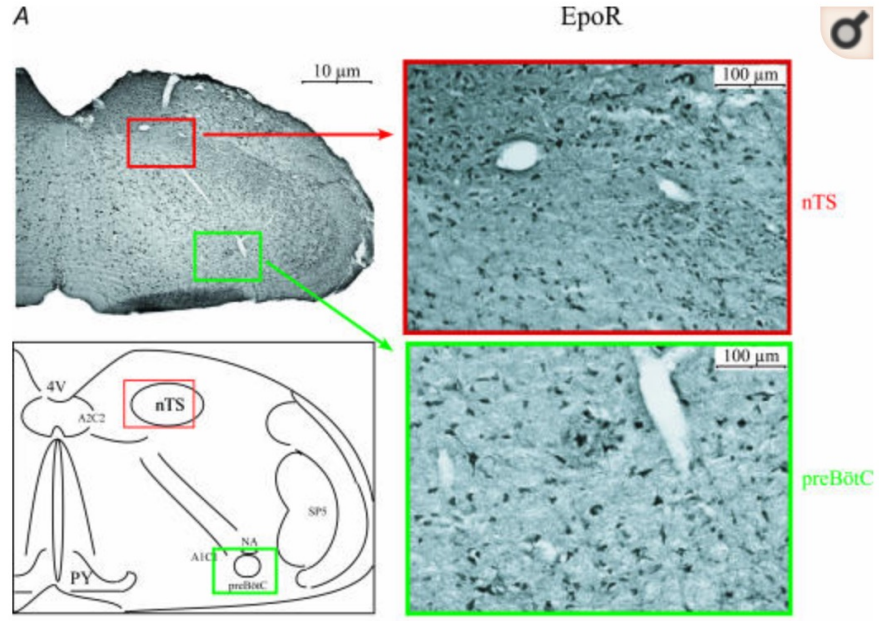
Villafuerte et al. JAP 2016

The secrets of Epo?

Epo and ventilatory control

- **Overexpression of Epo in mice increase minute ventilation during severe hypoxia (Tg21 mice)**
- **Proof of EpoR in cerebral areas implied in ventilatory control: Nucleus Tractus Solitarii (nTS) and the pre-Bötzinger complex (preBotC)**

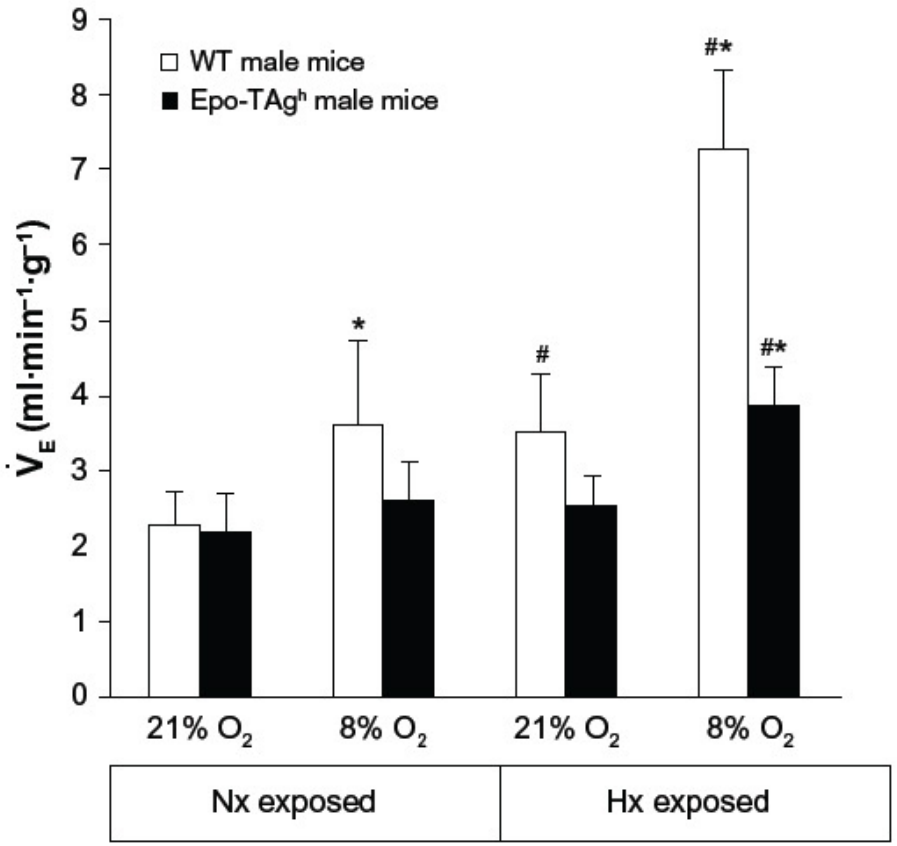




Soliz et al. 2005 J Physiol

Epo and ventilatory control

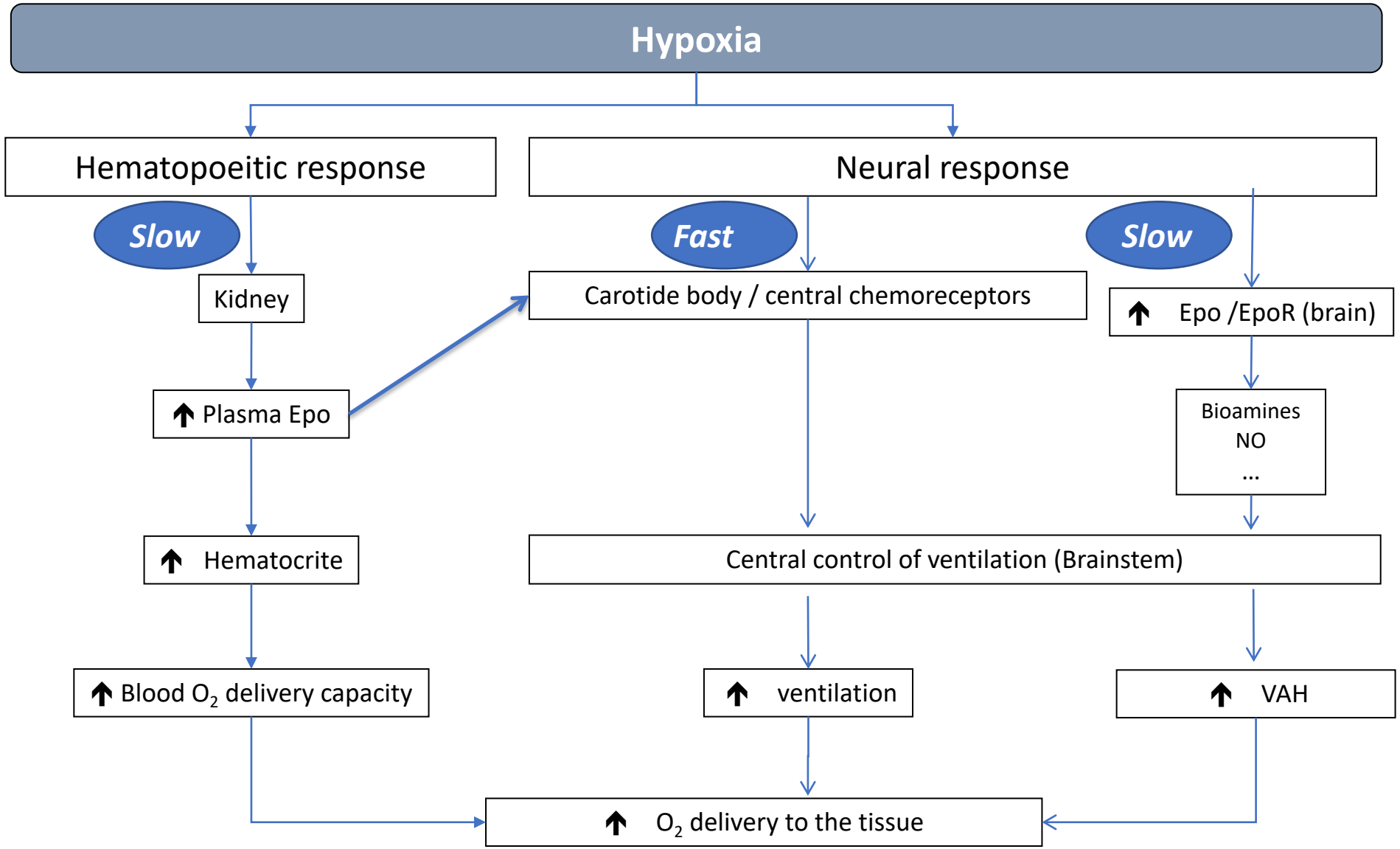
- **Lower ventilation in male EpoTAgh mice in hypoxia**
- **No ventilatory acclimatization in male EpoTAgh mice**
- **Lack or limited ventilatory response to hypoxia even after chronic hypoxic exposure in male EpoTAgh mice**



Ventilatory response to hypoxia in Epo-TAgʰ mice. Minute ventilation measured in normoxia (F_IO_2 21%) or acute hypoxia (F_IO_2 8%) in WT (white bar) and Epo-TAgʰ (black bar) mice maintained in normoxic (Nx exposed) or hypoxic (14 days, Hx exposed) conditions. Epo-TAgʰmice had a normal ventilation at rest, did not display ventilatory acclimatization to hypoxia, and did not respond to acute hypoxia even after the exposure to chronic hypoxia. Values are expressed as mean ± SD. *P<0.05 21% O_2 vs 8% O_2; #P<0.05 Nx exposed vs Hx exposed, same strain, same F_IO_2. Adapted from Voituron N, Jeton F, Cholley Y, et al. Catalyzing role of erythropoietin on the nitric oxide central pathway during the ventilatory responses to hypoxia. **Abbreviations:** Epo, erythropoietin; Epo-TAgʰ mice, Epo-deficient mice; Hx, hypoxia; Nx, normoxia;

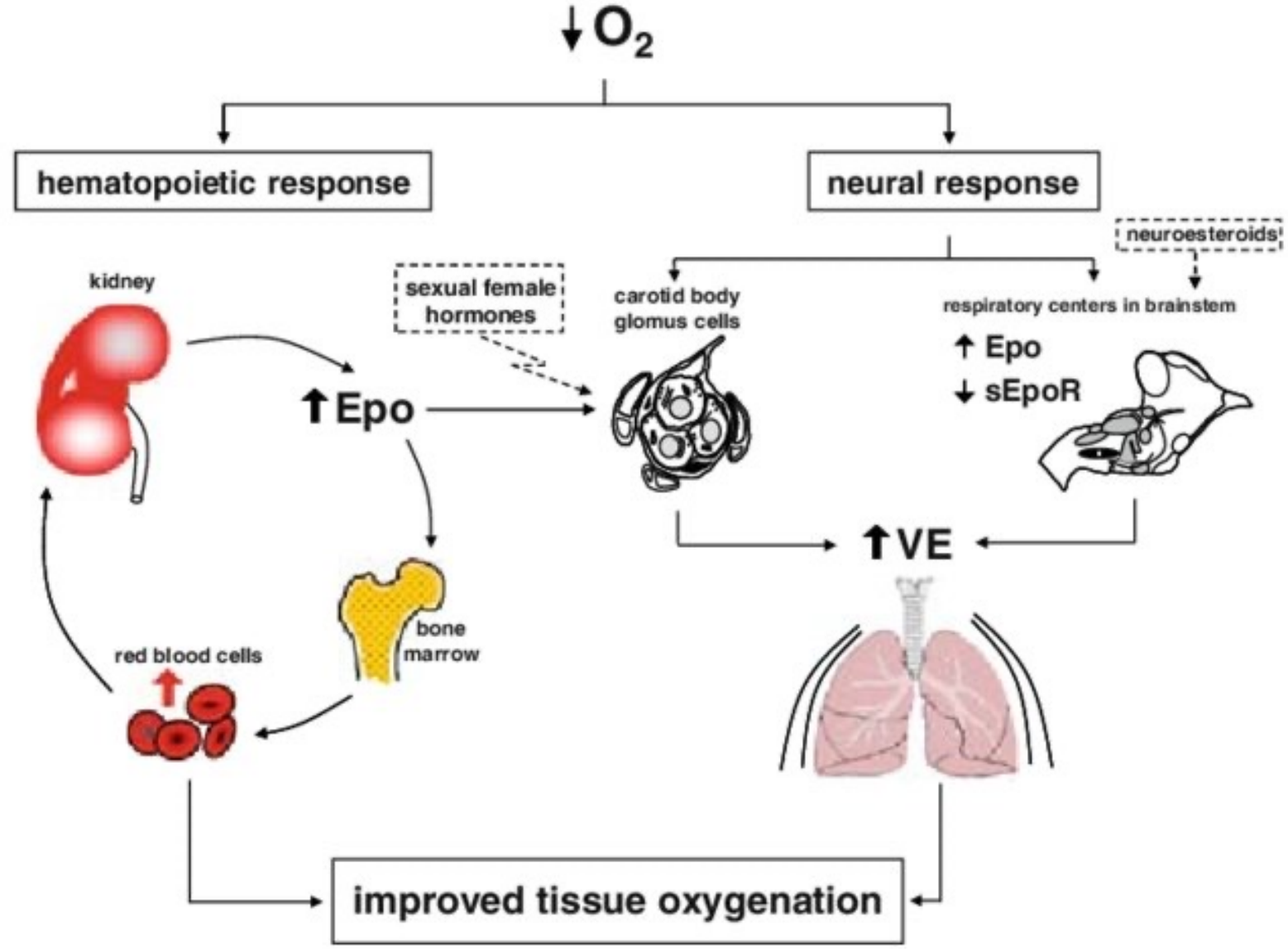
Voituron et al. 2014; Pichon et al. 2016

Epo and ventilatory control



Soliz et al. 2007 J Physiol

Epo and ventilatory control

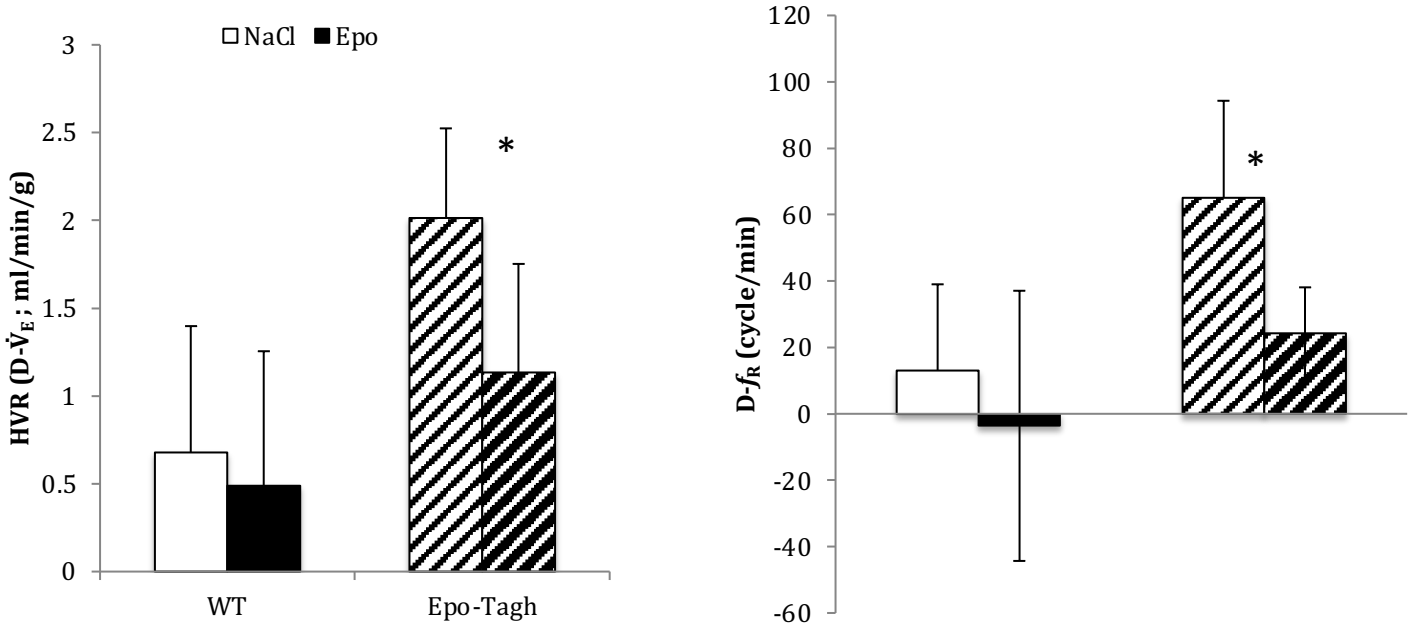


Gasmann & Soliz 2009 J Physiol

Epo and ventilatory control

- **Intrathechal injection of Epo decrease the hypoxic ventilatory response (HVR) in female Epo deficient mice (EpoTagh mice)**
- **Interaction of Epo with sexual hormone in mice**

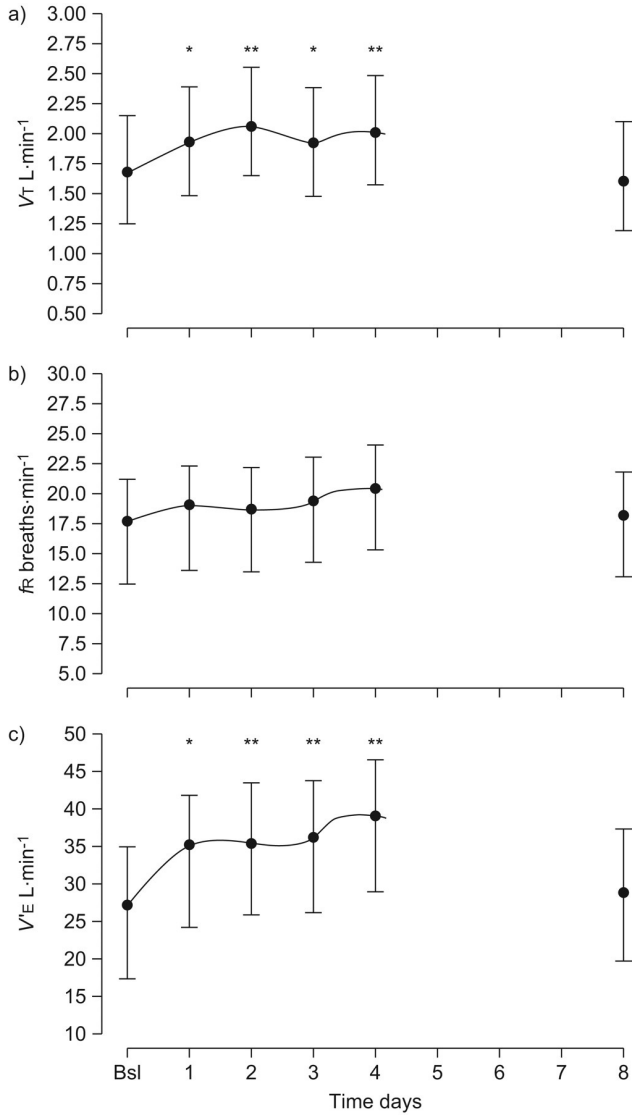
Femelles

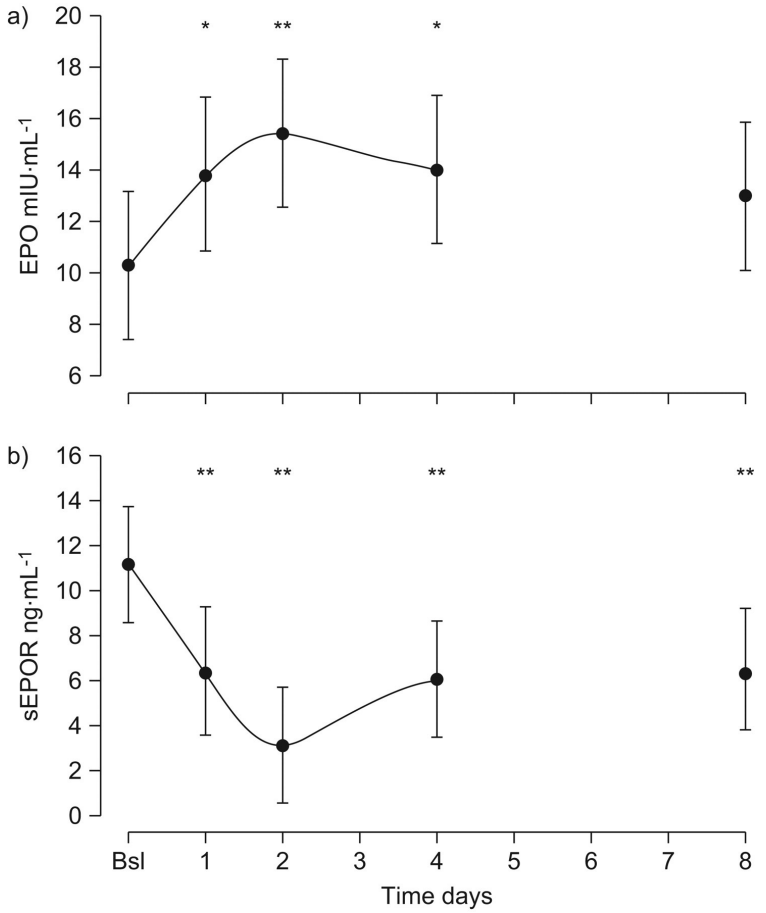


Jeton et al. 2017 Respir Physiol Neurobiol

Epo and ventilatory control

- **Suggested relationship between ventilatory acclimation after intermittent hypoxic exposure and Epo and sEpo-R expression in human**





Brugniaux et al. ERJ 2011

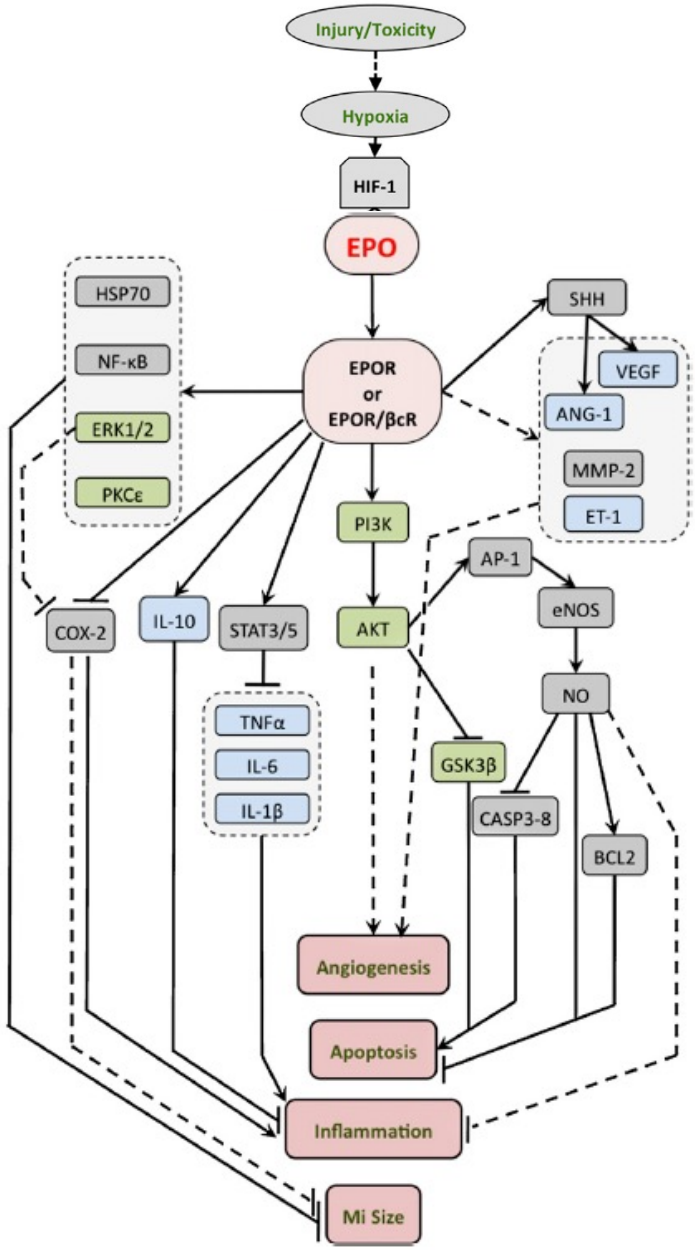
The secrets of Epo?

Cardioprotection

- **Pluripotent effect of Epo and Epo-R in non hematopoietic tissues.**

- **During hypoxia, apoptosis and inflammation ⇧ expression of Epo and EpoR in the cardiovascular system and could induce:**

  - ➔ **Angiogenesis**
  - ➔ **Anti apoptotic effects**
  - ➔ **Anti inflammatory effects**
  - ➔ **Myocardial infarct size reduction**



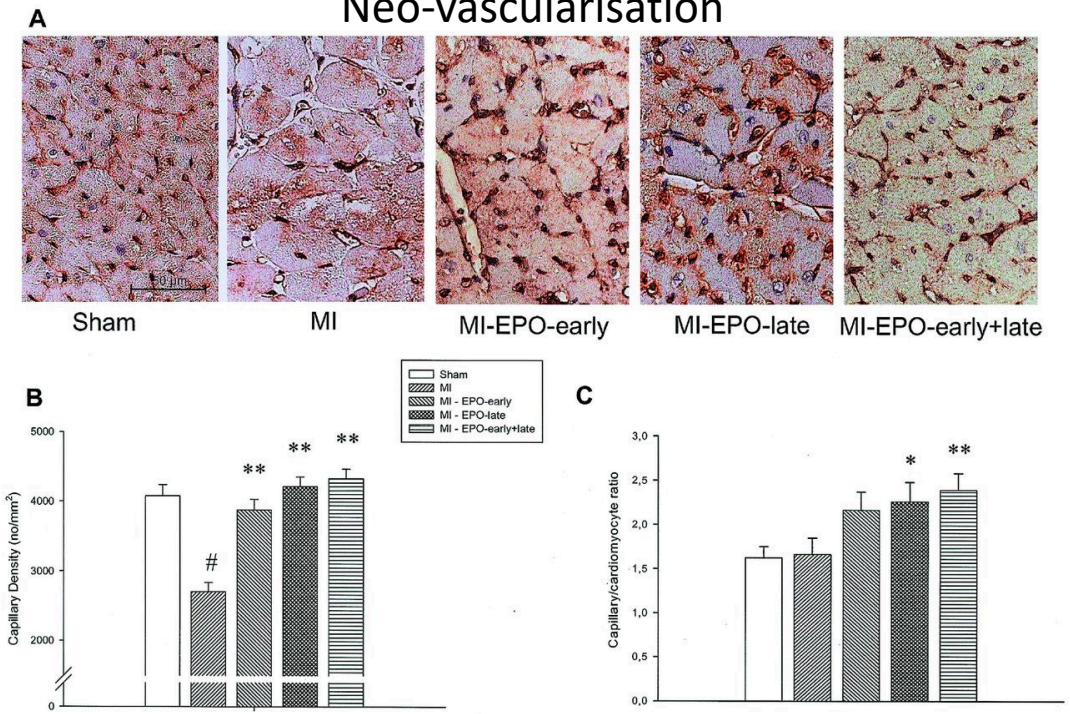
Chateauvieux et al. 2011 Biochem Pharama

Cardioprotection

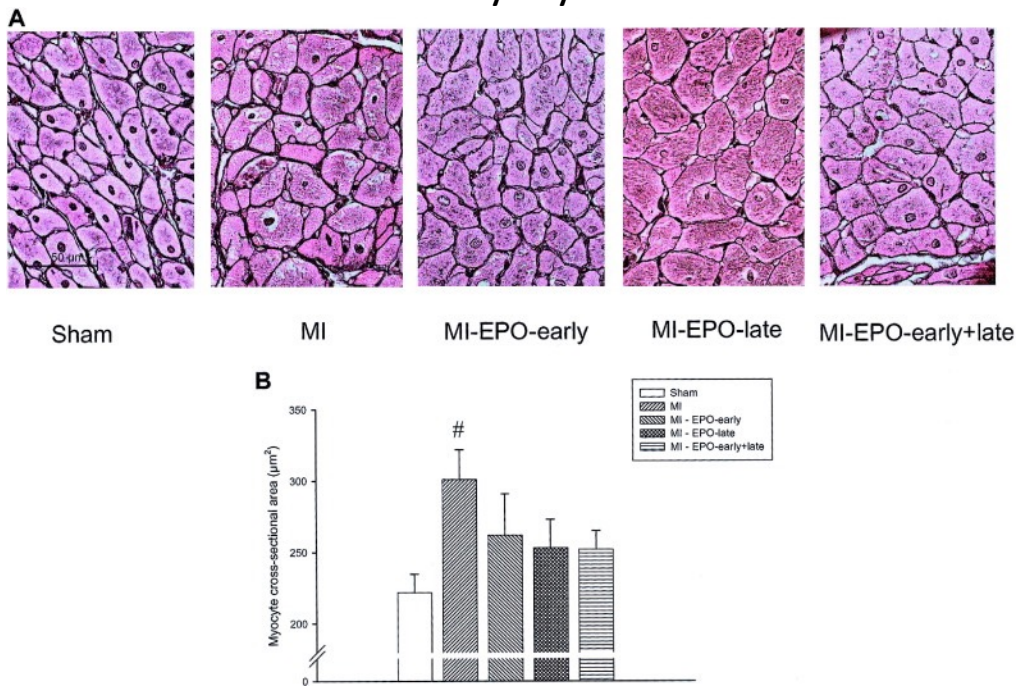
Significant effect of Epo treatment on myocardial infarct size:

- ➔ **angiogenesis (⇧ capillary density)**
- ➔ **neovascularisation**

Neo-vascularisation



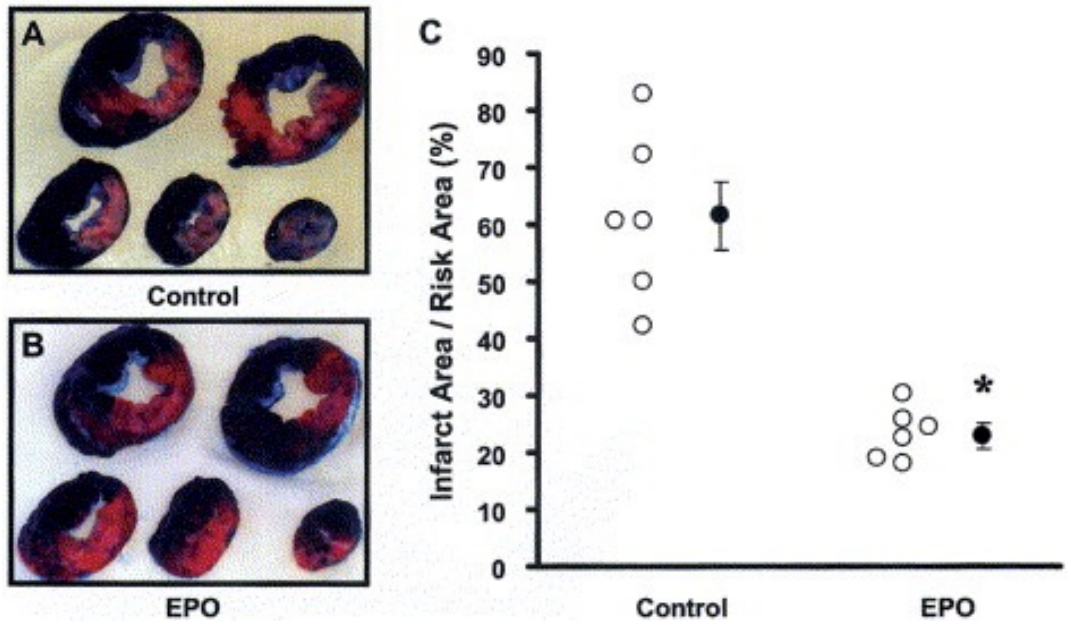
Cardiomyocyte area

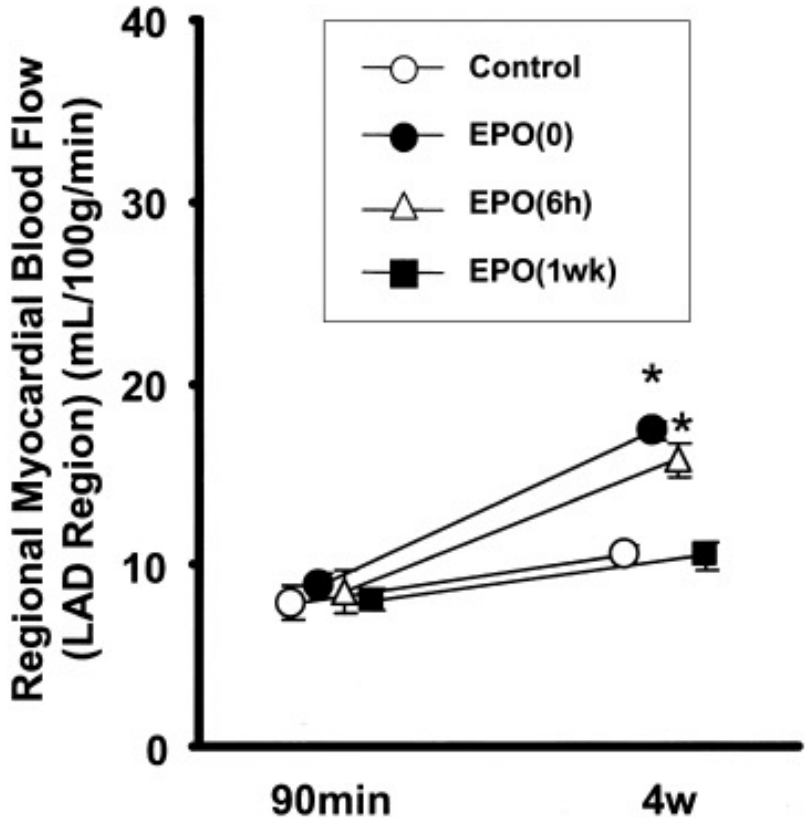


Sanchis-Gomar et al. 2014
van der Mee et al. 2005 JACC

Cardioprotection

Significant effect of early treatment of Epo to reduce myocardial infarct size and restore blood flow:



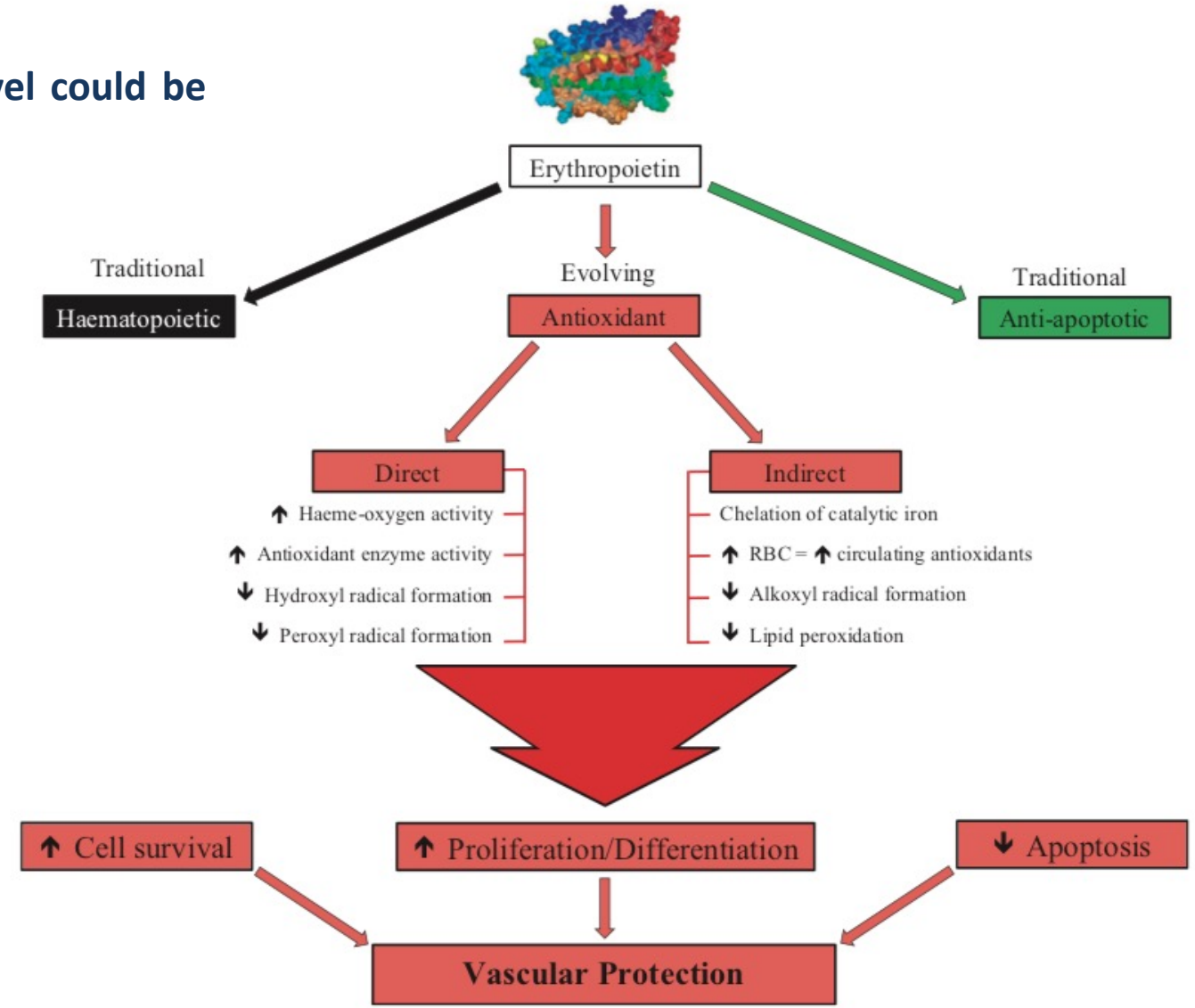


Hirata et al. 2006 JACC

The secrets of Epo?

Antioxydant properties

- **Protective effects at the cardiovascular level could be due to the antioxidant properties of Epo**

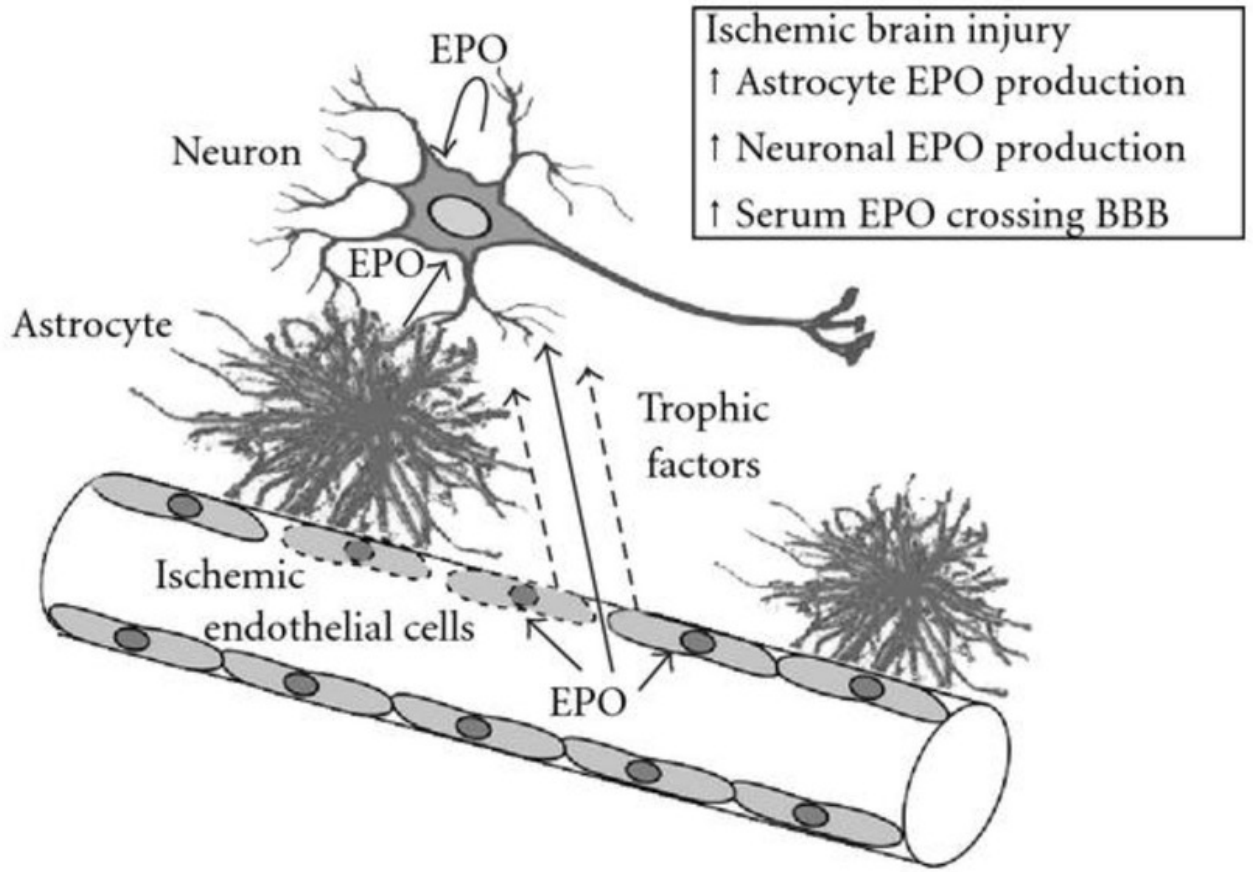


Brugniaux 2014 Acta Physiol
Bailey et al. 2014 Acta Physiol

The secrets of Epo?

Neuro-protection

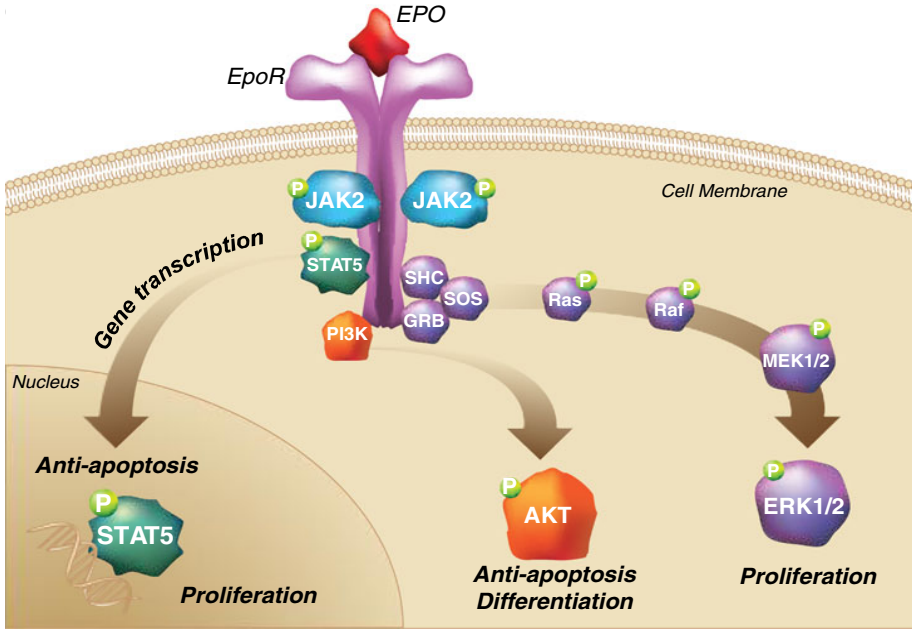
- **Epo synthesis in the CNS** (astrocytes and neurones)
  (Gassmann, 2003 ; Jelkmann, 2007)



Alnaeeli al. 2012

Neuro-protection

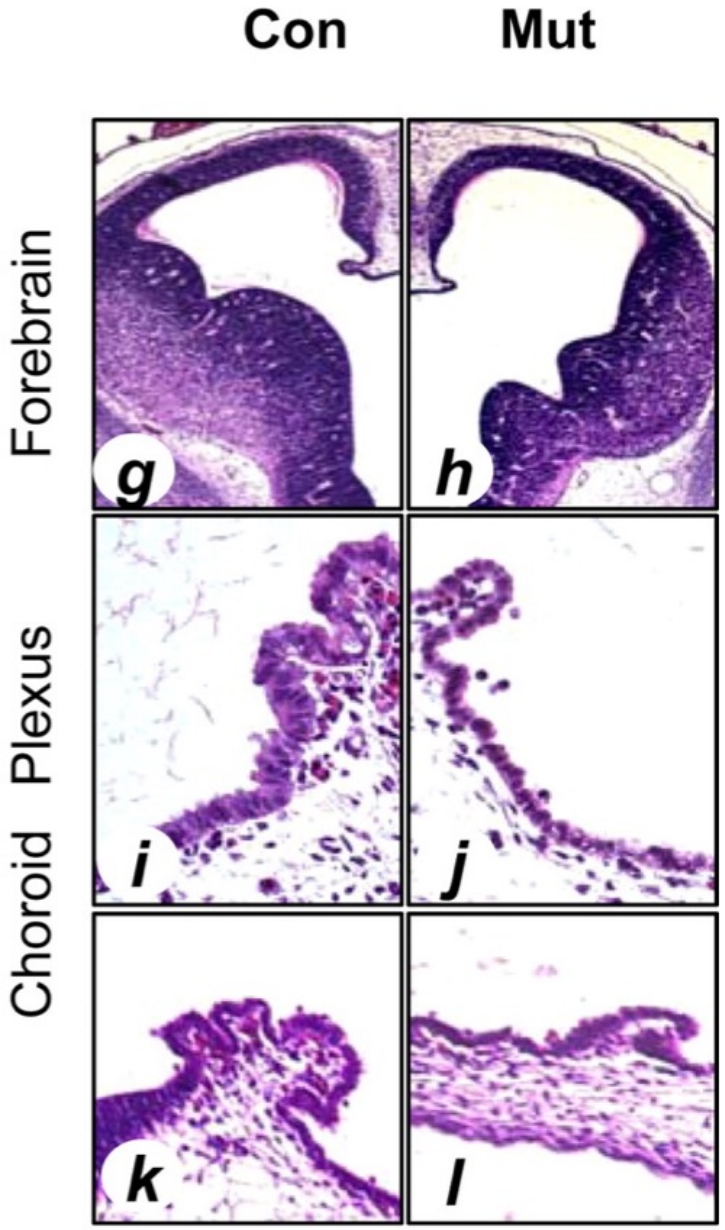
- **Acute neuroprotective effect of Epo:**
  - Antiapoptotic effect
  - Anticytotoxic effect
  - Antiinflammatory



Elliott, 2014

Neuro-protection

- **Evidence of Epo and EpoR are mandatory for normal CNS development**
- **Major effect for stroke recovery**



EpoR−/− mice

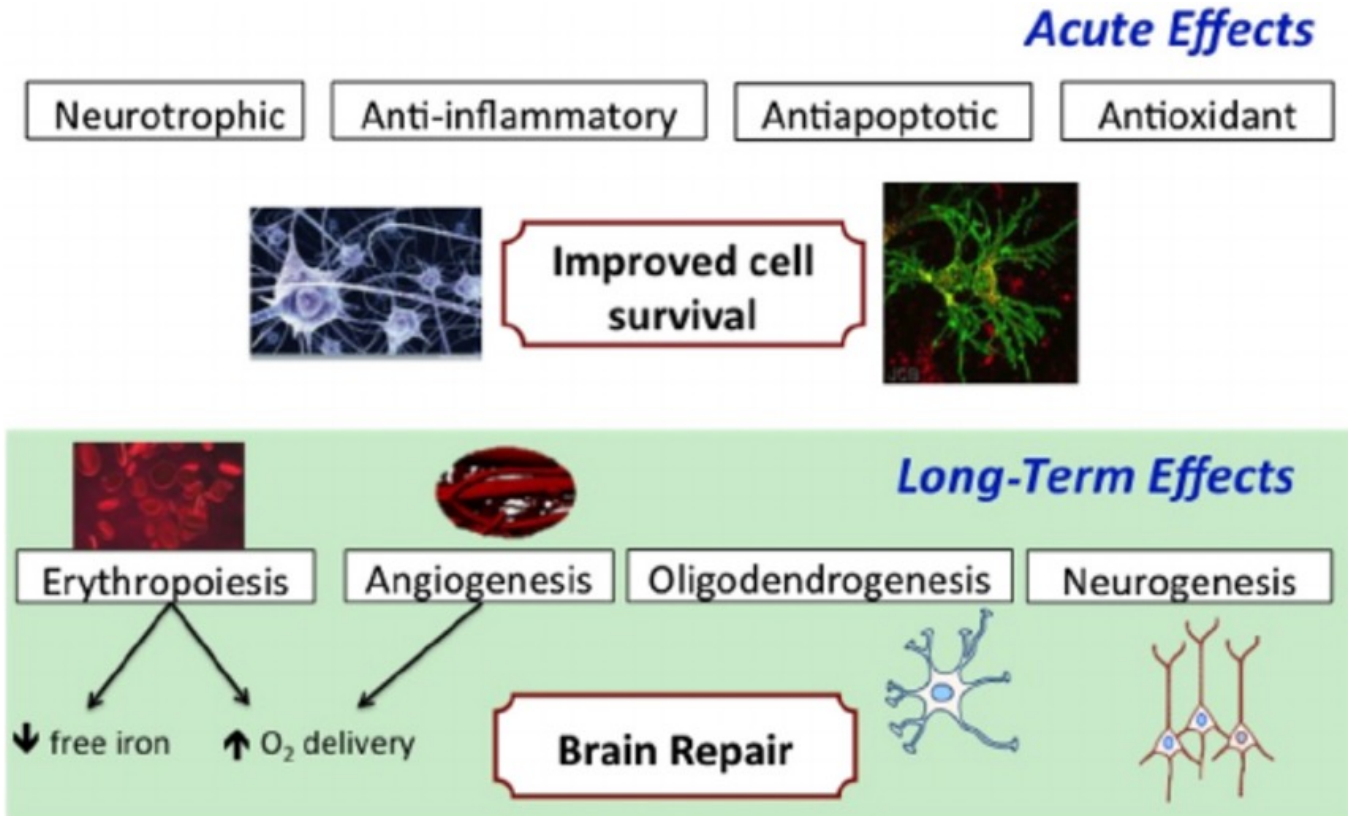
Epo−/− mice

Peter et al. J Neuro 2006

Neuro-protection

- **Major effect on long term treatment by Epo for CNS recovery by improvement in**

  ➔ Neurogenesis
  ➔ Oligodendrocytes genesis
  ➔ Angiogenesis



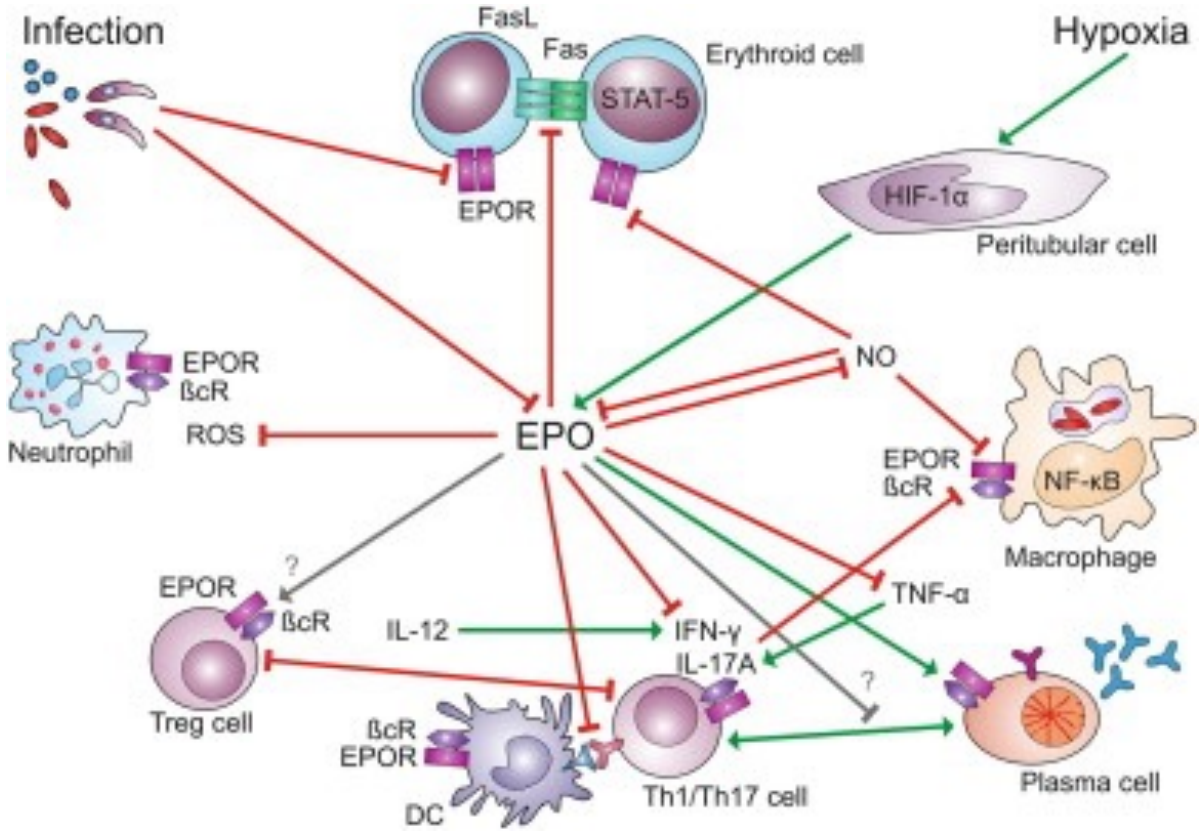
Jull et al. J 2012

The secrets of Epo?

Immun system and infection

- **Effect of Epo on inflammatory and immune actors:**
  - ➔ **Macrophages**
  - ➔ **Neutrophils**
  - ➔ **Lymphocytes B**
  - ➔ **Lymphocytes C**

- **Positive effects of Epo treatment on some auto-immune diseases (Crohn disease…)**

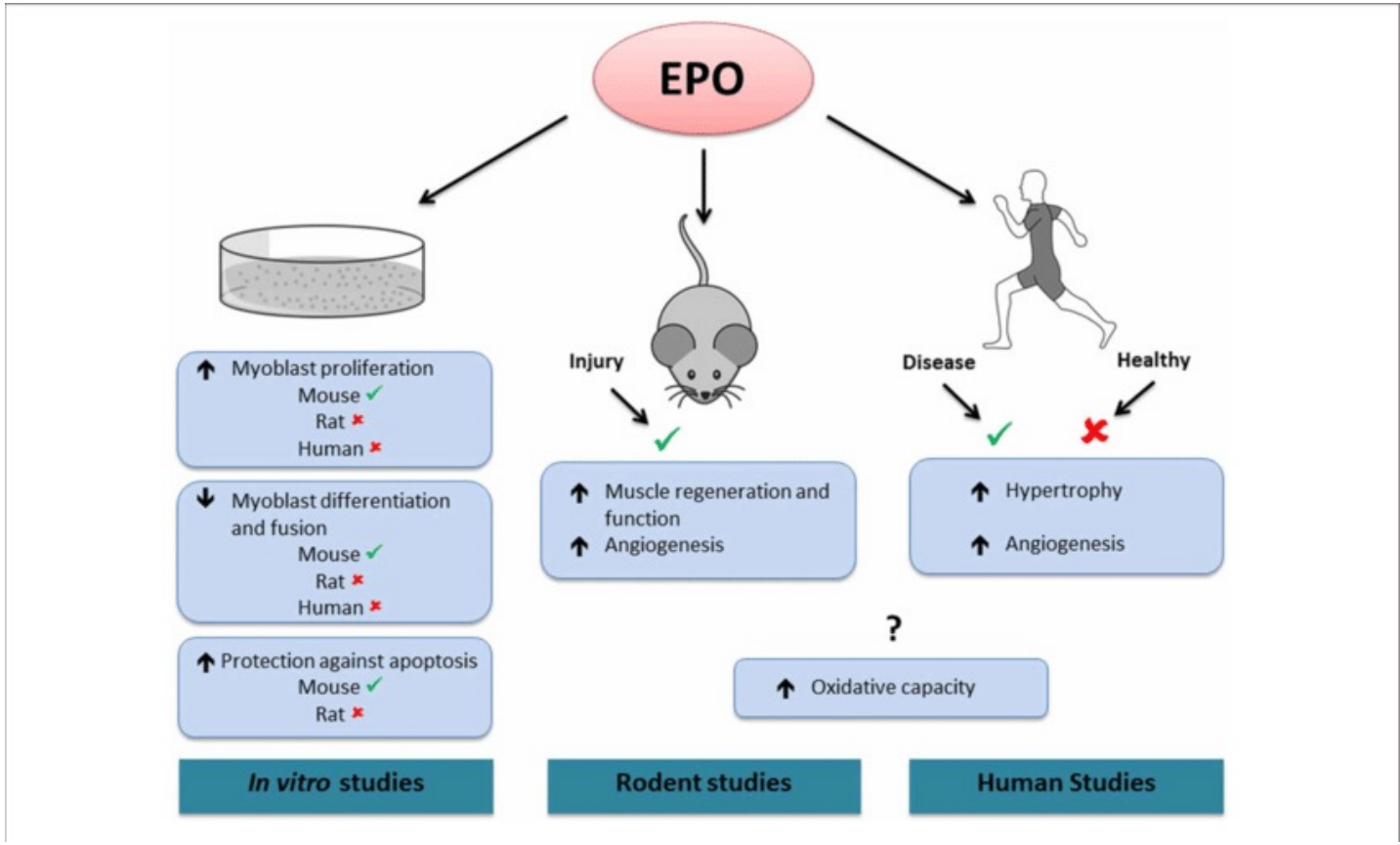


Nairz et al. 2012 Microbes and Infection

The secrets of Epo?

Muscular functions

- **Positive effects of Epo on muscular functions have been proposed:**
  - ➔ **Improve proliferation and differentiation in mice muscles**
  - ➔ **Reduce apoptosis**
  - ➔ **Increase satellite cells numbers**
  - ➔ **Improve muscle regeneration**
  - ➔ **Improve angiogenesis**
  - ➔ **Improve hypertrophy**

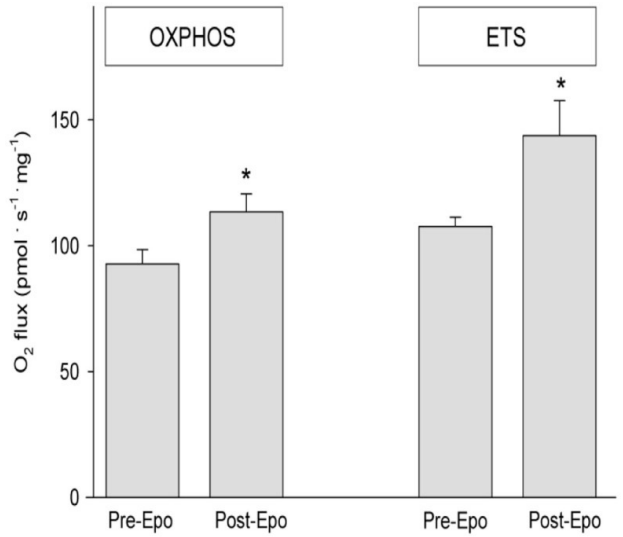


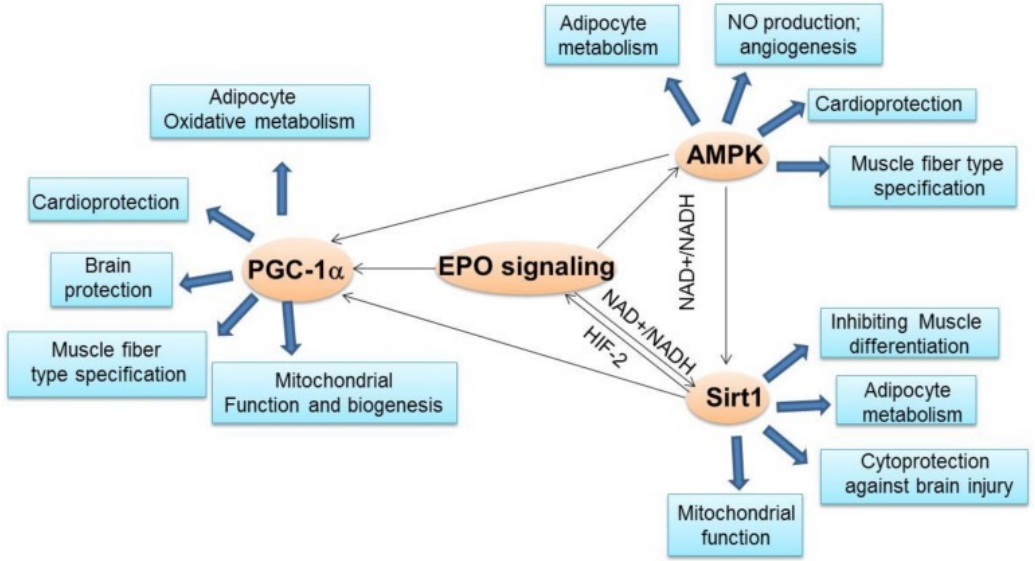
Scoppetta & Grassi 2004
Hagström et al. 2010
Lamon et Russell 2013

The secrets of Epo?

Metabolism

- **Positive effect of Epo/EpoR on metabolism:**
  - ➔ **Higher EpoR density in the white adipose tissue (60% hematopoietic tissue)**
  - ➔ **dDecrease in EpoR → obesity in KO mice**
  - ➔ **Epo/EpoR implied in the glucose tolerance and insulin sensitivity**
  - ➔ **Epo seems to improve muscular oxidative metabolism**



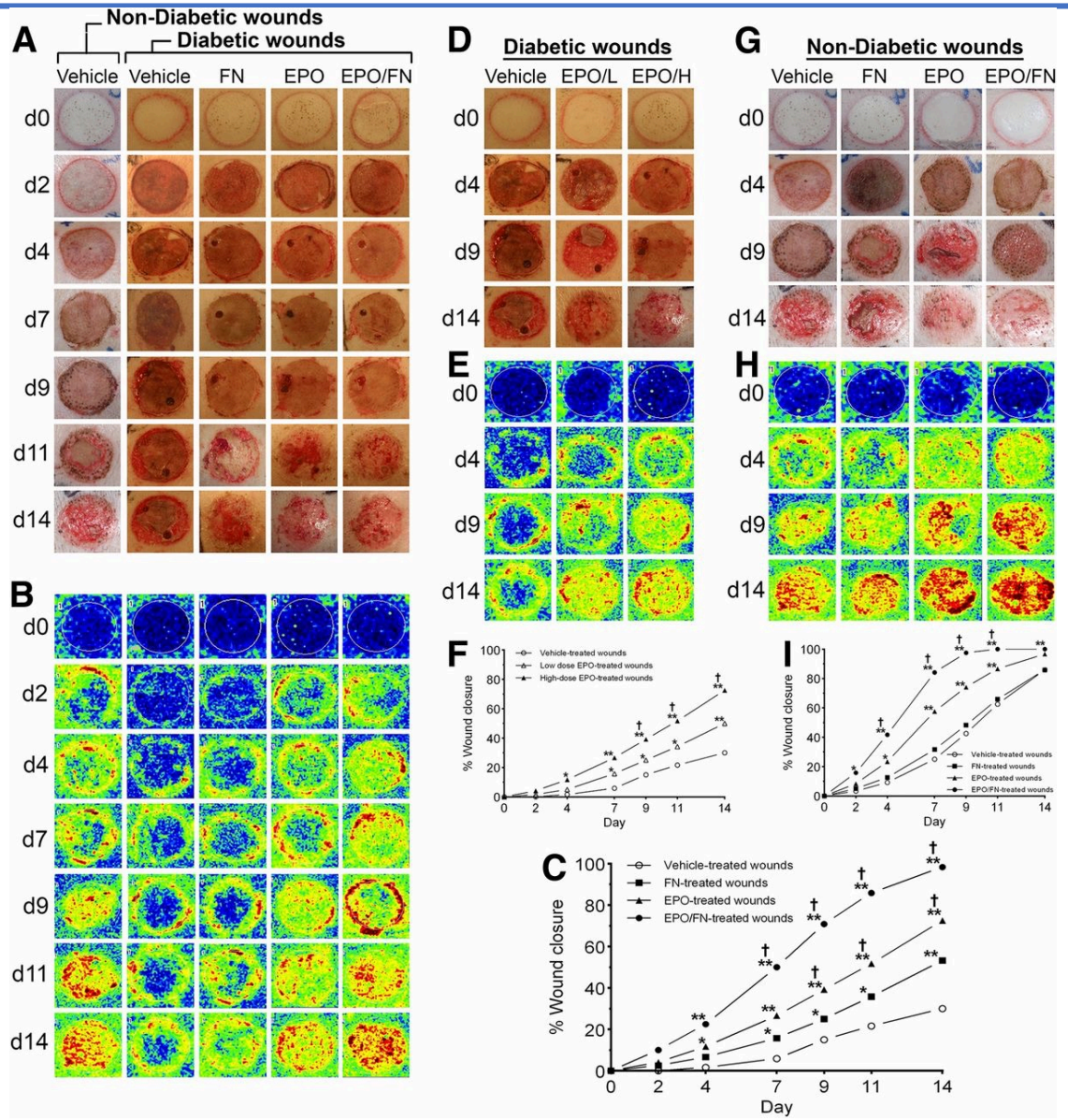


Wang et al. 2014 Int J Biol Sci
Plenge et al. 2012 Front Physiol

The secrets of Epo?

Healing

- **Accelerating action of EPO on the healing of the burn injury in normal and diabetic subjects**
- **Dose effect of Epo treatment with an improvement in capillarization and blood flow (red color)**

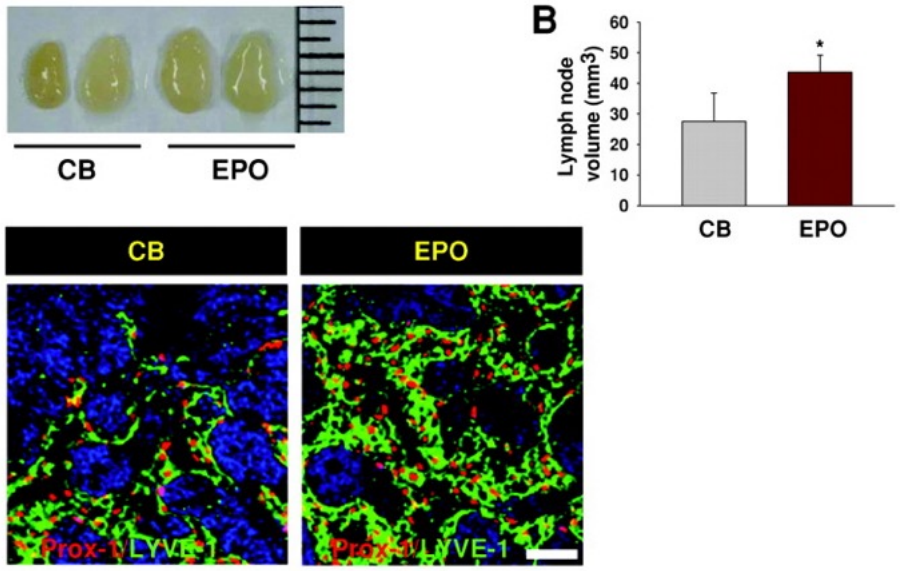


Hamed et al. 2017 Diabetes

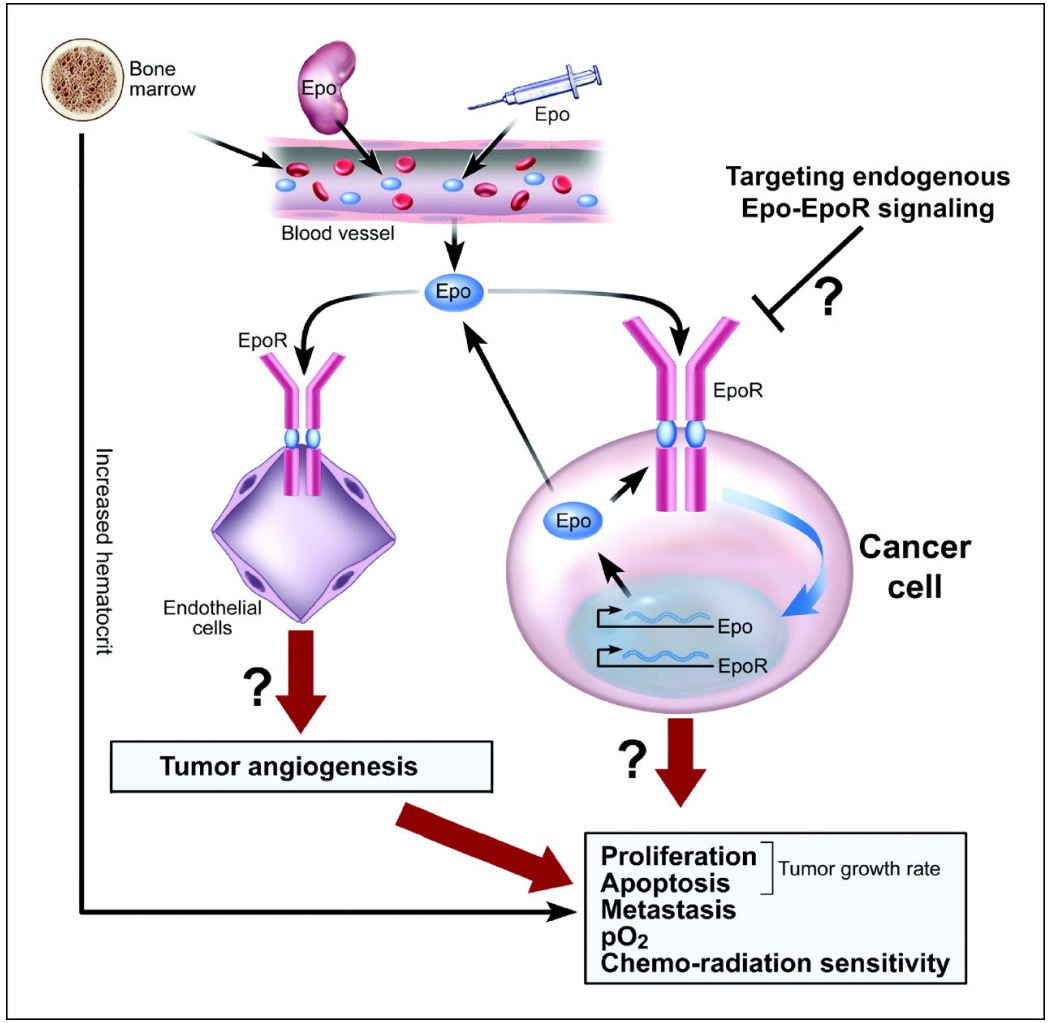
Dark side of Epo?

Deleterious effects of Epo

- **Pro tumoral and pro metastatic effects of Epo (and hypoxia …)**
- **Increase the volume of lymph node tumors**



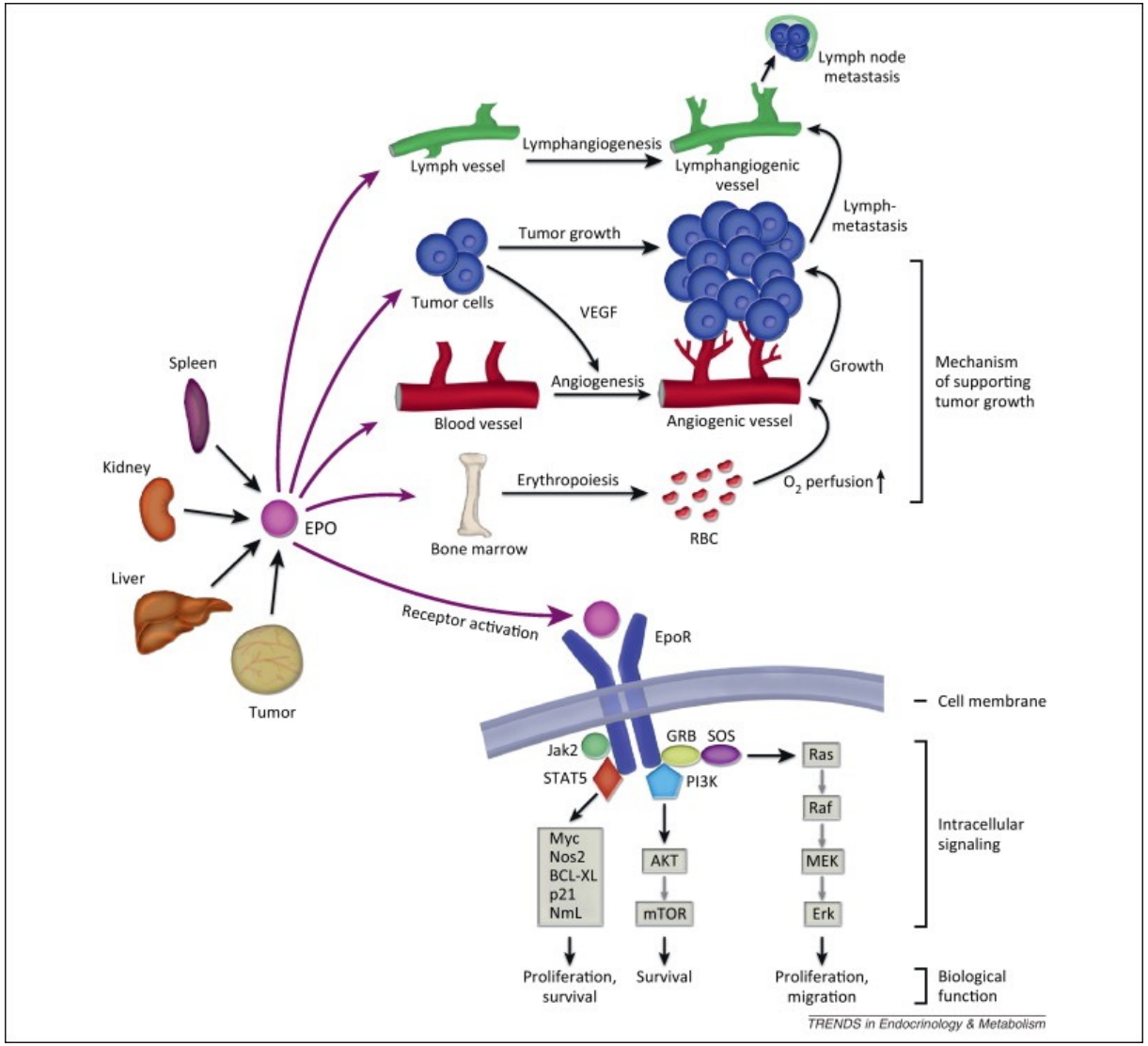
Matthew et al. 2006 Diabetes
Lee et al. 2011



Deleterious effects of Epo

- **Positive/negative effect discussed in the treatement of some cancer**

« Erythropoietin in cancer : a dilemma in risk therapy »



Cao et al. 2013

Deleterious effects of Epo

Use of Epo in chronic treatment for chronic kidney disease or anemia conduce to:

- **Metastasis and pro tumoral effects**
- **Hypertension**
- **Thrombo-embolism…**

➔ Use of new forms of Epo without erythroid effects

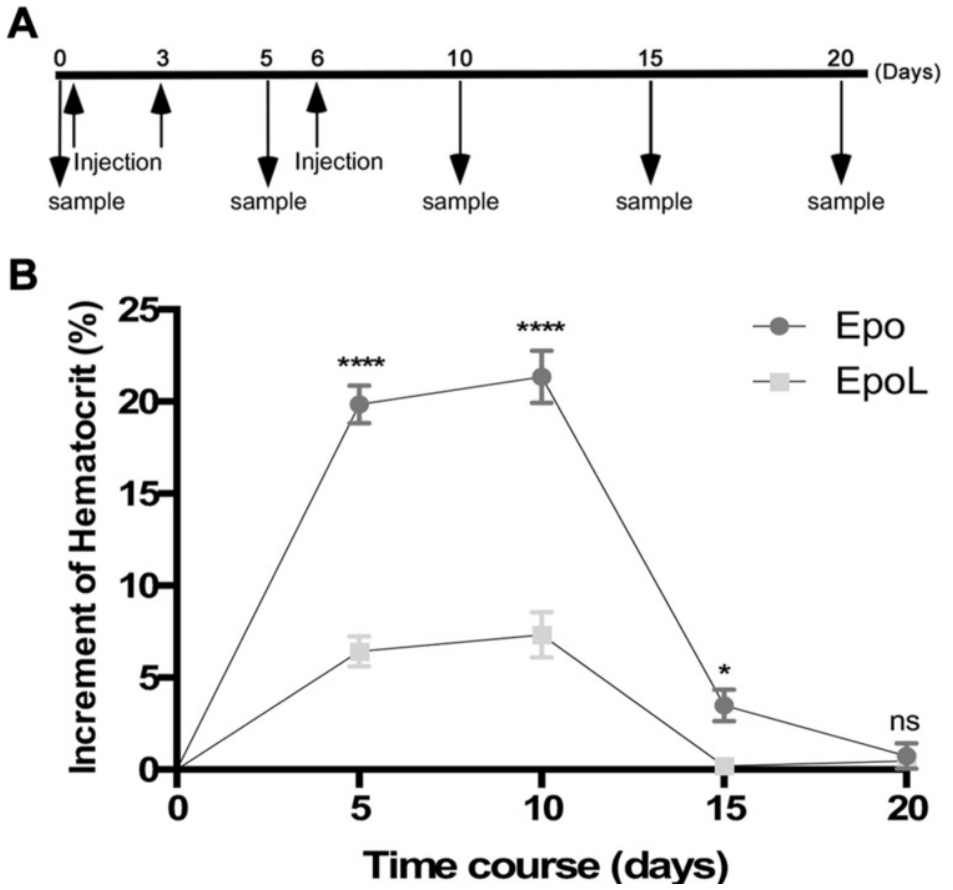
➔Use of Hypoxia-inducible factor (HIF) prolyl hydroxylase (PH) enzyme inhibitors (Roxadustat, Vadadustat…)

Cao et al. 2013; Gupta & Wish 2017

New Epo

Use of variant Epo with low glycosylation and without hematopoietic effect (EpoL) reduce the hematopoietic effect

“ EpoL represents an important target to develop a potential biopharmaceutical to treat different central nervous system pathologies related to oxidative stress such as stroke or neurodegenerative diseases. ”



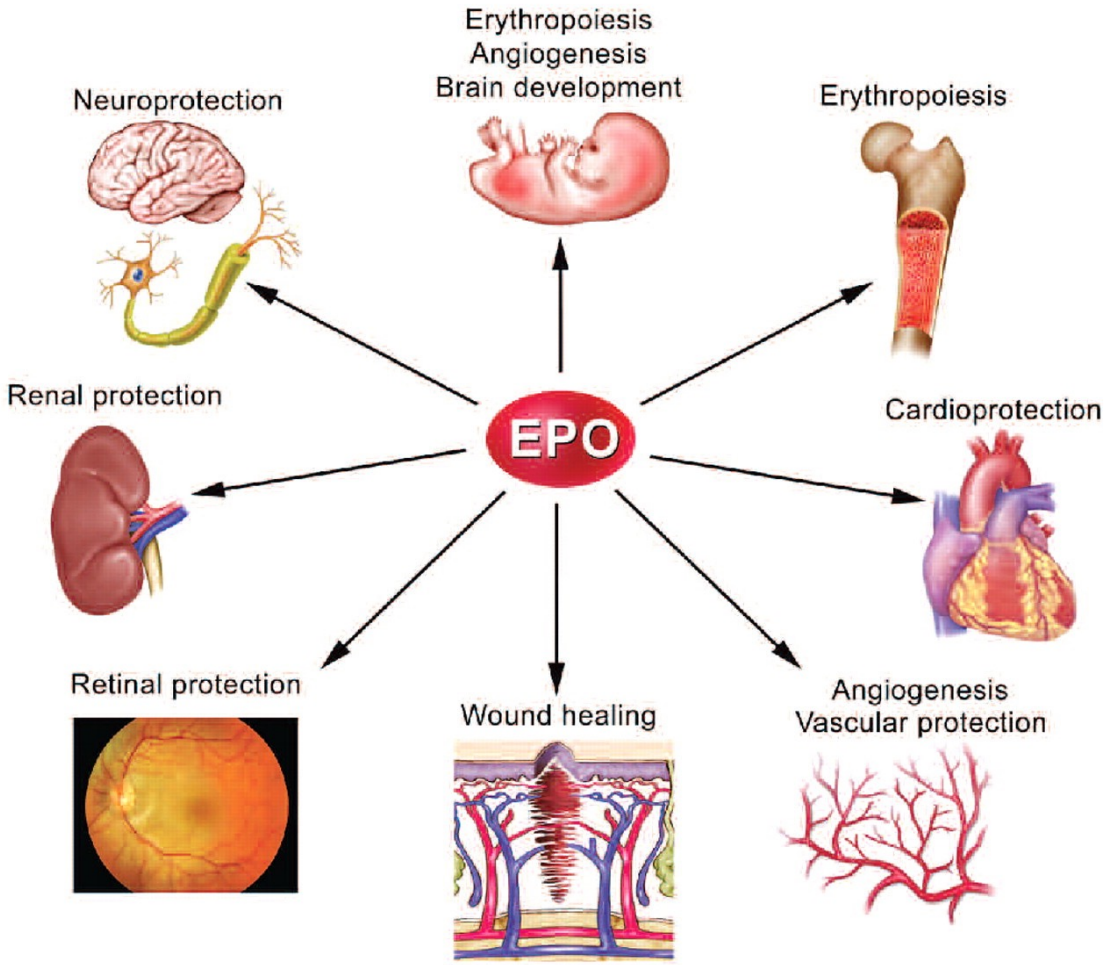
Castillo et al. 2018

Take home message

Pluripotent effects and protective effects of Epo on numerous tissues:

- ➔ **Heart**
- ➔ **Central nervous system**
- ➔ **Kidney**
- ➔ **Skin**
- ➔ **Cardiovascular system**
- ➔ **Eyes…**

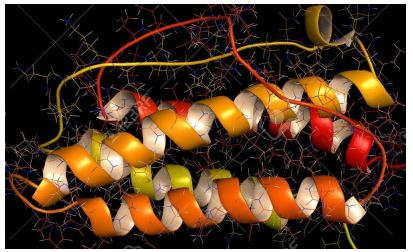
+ Effects of Epo as a mediator in immune system and cardio-respiratory responses to hypoxia



Cerami 2012 Ann Rheum Dis ; Manolis et al.

Merci !

Aurélien Pichon
@aurelien.pichon

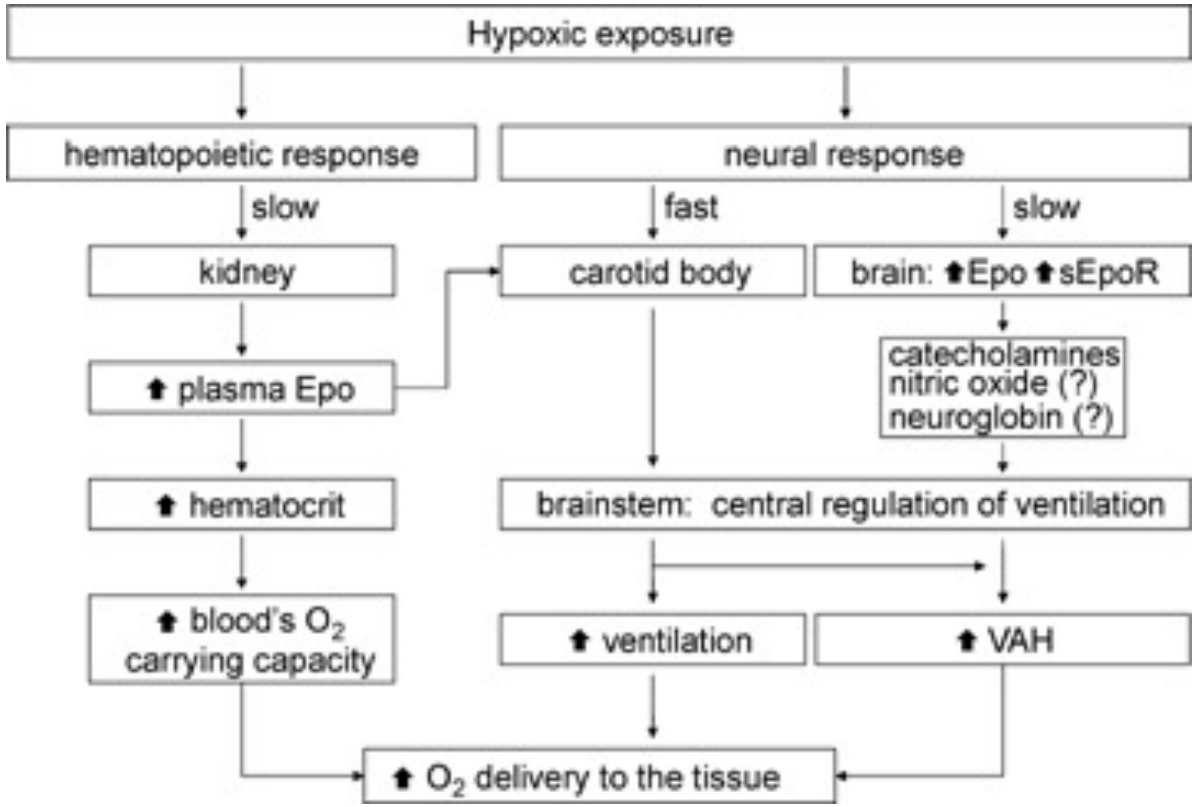


EpoTagh characteristics

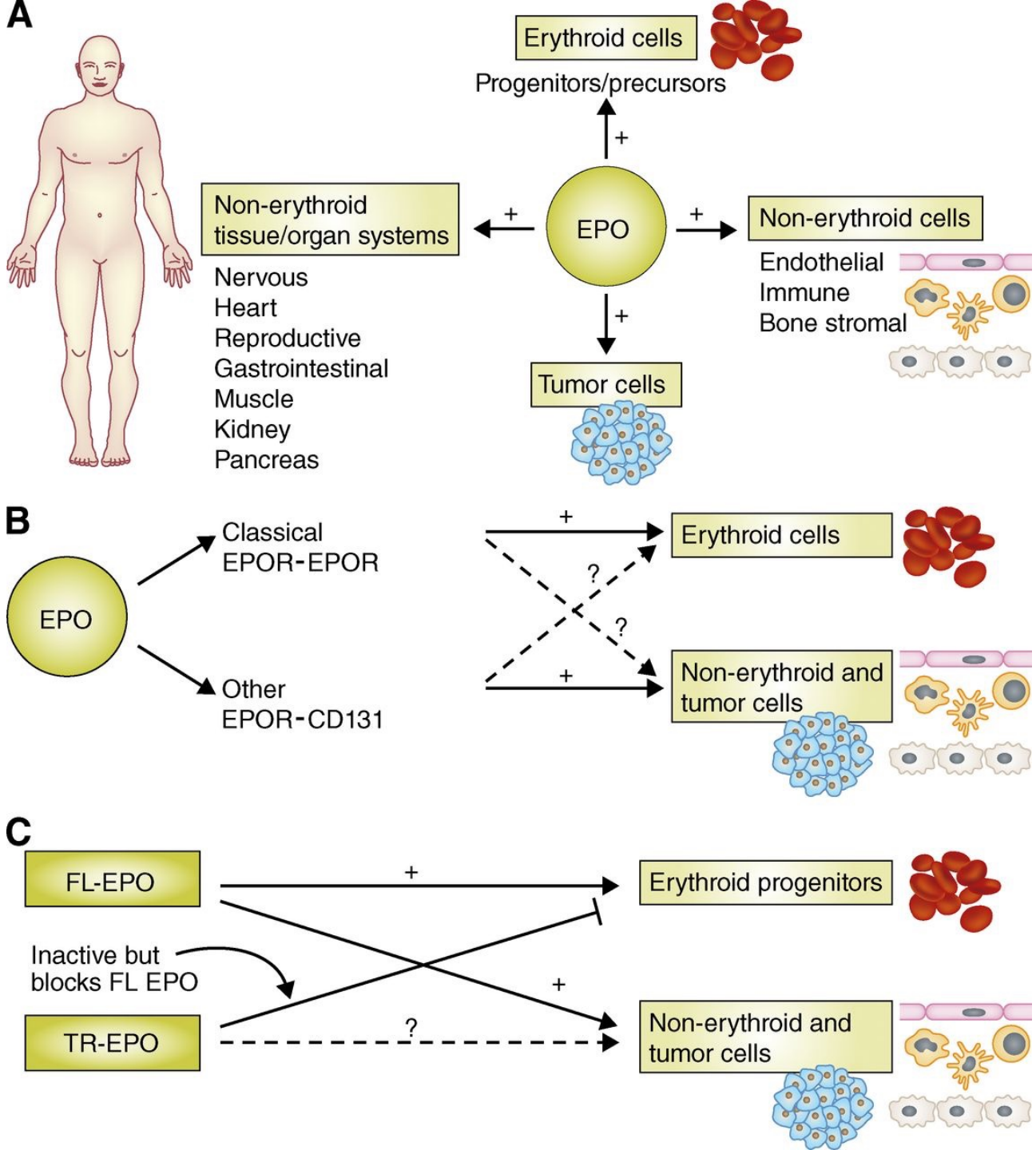
		References	Wild-type mice	Epo-TAg[h] mice
	Hemoglobin ($g \cdot dL^{-1}$)[b]	Macarlupu et al[81]	17.1±0.3	6.9±0.3[a]
	Hematocrit (%)[b]	Macarlupu et al[81]	54.2±0.8	24.0±1.6[a]
Cardiac characteristics	Heart rate (bpm)[c]	El Hasnaoui-Saadani et al[20]	500±27	548±46
	Stroke volume ($\mu L \cdot g^{-1}$)[c]	El Hasnaoui-Saadani et al[20]	1.9±0.19	3.2±0.68[a]
	Cardiac output ($mL \cdot min^{-1} \cdot g^{-1}$)[c]	El Hasnaoui-Saadani et al[20]	0.94±0.14	1.76±0.43[a]
	Systolic blood pressure (mmHg)[c]	El Hasnaoui-Saadani et al[20]	96.7±8.5	94.2±5.8
	Right ventricular weight (mg)[b]	Macarlupu et al[82]	23±1	33±2[a]
	Left ventricular and septum weight (mg)[b]	Macarlupu et al[82]	80±2	113±3[a]
	Fulton ratio[b]	Macarlupu et al[82]	0.288±0.013	0.297±0.010[a]
Ventilatory parameters	Minute ventilation ($mL \cdot min^{-1} \cdot g^{-1}$)[c]	Voituron et al[90]	2.26±0.48	2.17±0.53
	Respiratory frequency ($c \cdot min^{-1}$)[c]	Voituron et al[90]	261±34	284±54
	Tidal volume ($\mu L \cdot g^{-1}$)[c]	Voituron et al[90]	8.63±1.26	7.62±1.09
	Resting oxygen consumption ($mL \cdot min^{-1} \cdot kg^{-1}$)[b]	Macarlupu et al[81]	93.3±4.7	96.8±6.5
	Maximal oxygen consumption ($mL \cdot min^{-1} \cdot kg^{-1}$)[b]	Macarlupu et al[81]	270.7±22.0	210.2±12.3[a]

Pichon et al. 2016

Soluble erythropoietin receptor is present in the mouse brain and is required for the ventilatory acclimatization to hypoxia



The Journal of Physiology, Volume: 583, Issue: 1, Pages: 329-336, First published: 07 August 2007, DOI: (10.1113/jphysiol.2007.133454)



Multifaceted effects and targets of EPO. (A) EPO targets many cell types and tissues, including erythroid cells and their progenitors, tumor cells, and a variety of other nonerythroid cells and tissues. (B) EPO signals in erythroid cells via EPOR-EPOR homodimers and in nonerythroid cells via EPOR-CD131 heterodimers. (C) The effects of full-length EPO (FL-EPO) on both erythroid and nonerythroid cells may be blocked by DPP4-truncated EPO (TR-EPO), which itself may lack biological activity depending on which EPOR it targets. +, stimulating effect; ?, action/function not yet known.

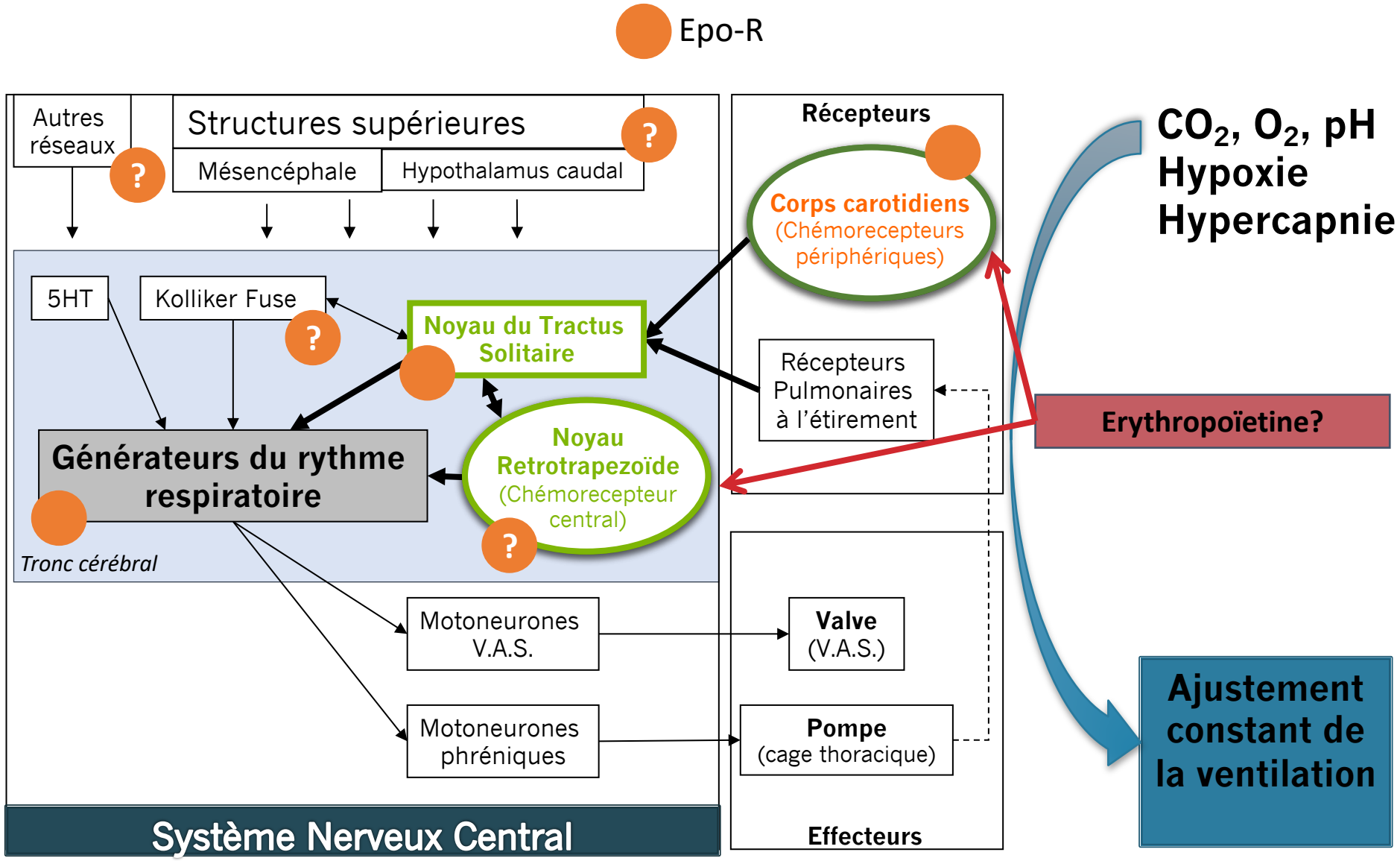
JEM Home » 2013 Archive » 11 February » 210 (2): 205

Minireview

Erythropoietin: multiple targets, actions, and modifying influences for biological and clinical consideration

Hal E. Broxmeyer

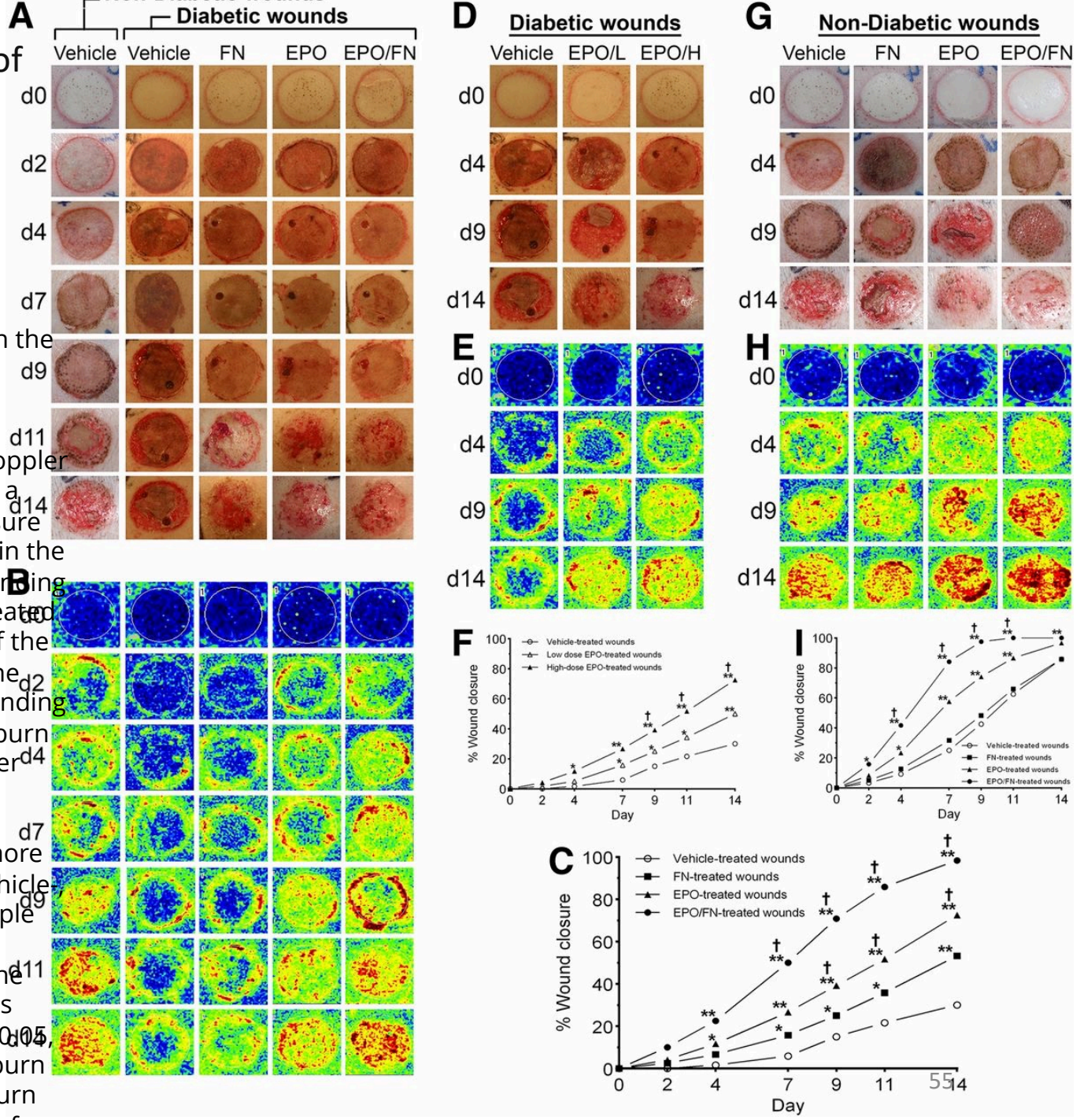
Régulation de la ventilation



Jeton et al.

Topical Erythropoietin Treatment Accelerates the Healing of Cutaneous Burn Wounds in Diabetic Pigs Through an Aquaporin-3–Dependent Mechanism

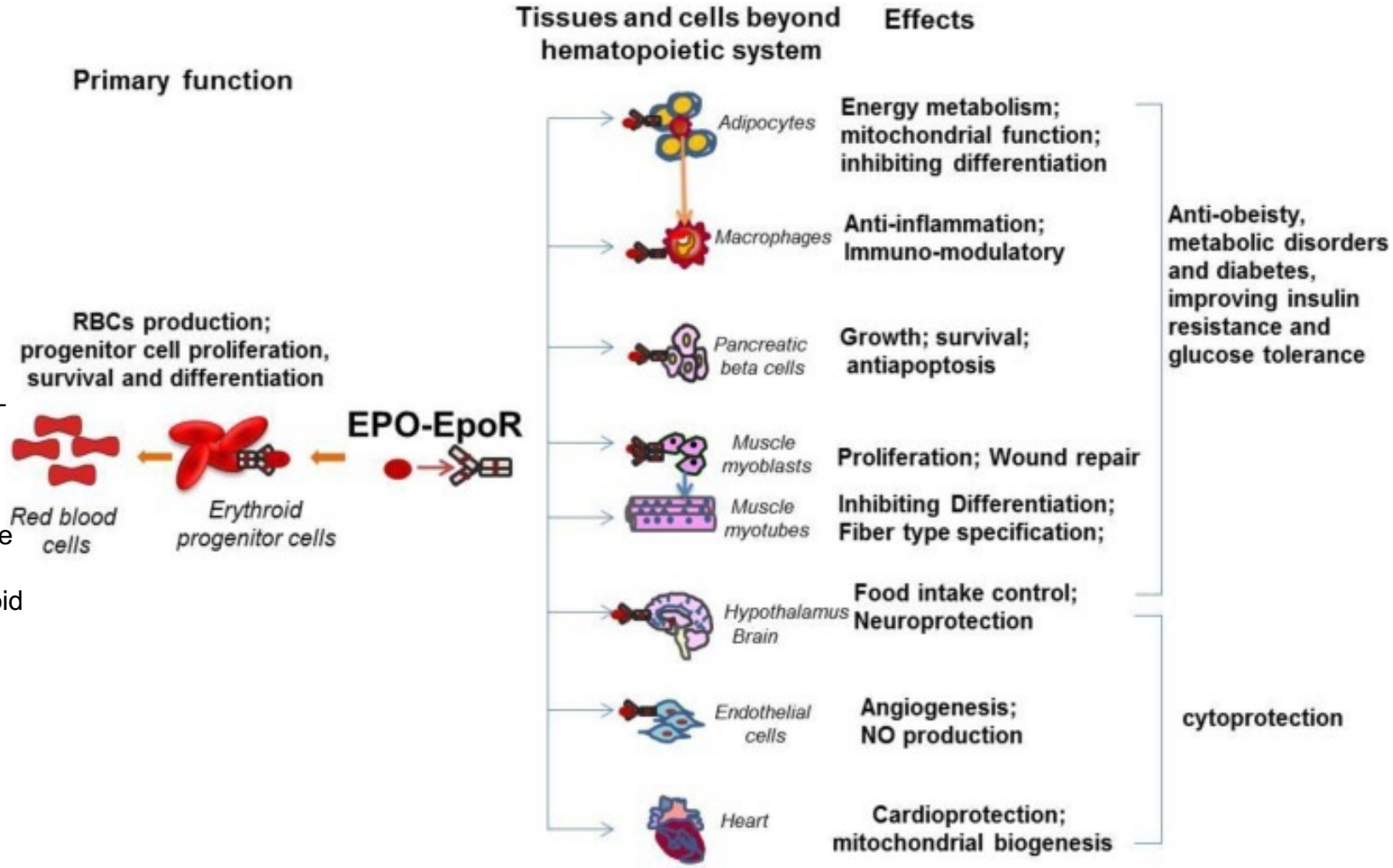
Diabetes 2017 Aug; 66(8): 2254-2265. https://doi.org/10.2337/db16-1205



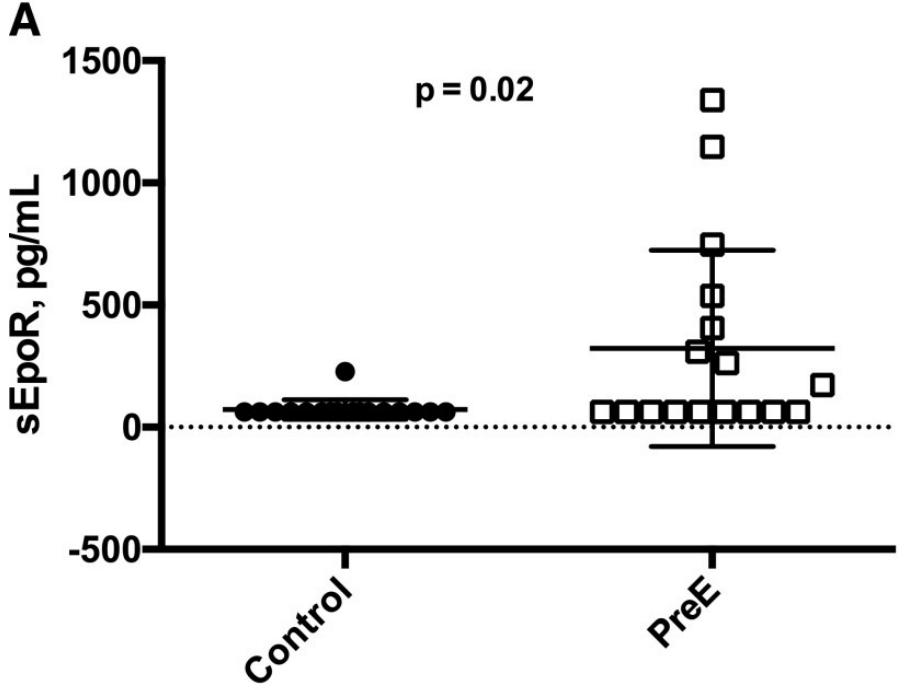
Topical EPO application accelerates wound closure and increases blood flow in the regenerating skin of diabetic wounds in a dose-dependent manner; an effect potentiated by FN. In the regenerating skin of nondiabetic wounds, topical application of FN does not affect wound closure and blood flow rates. Representative set of photographic images (*A*) and the corresponding laser Doppler scans (*B*) of a vehicle-, an FN-, an EPO-, and an EPO/FN-treated burn wound in a nondiabetic and diabetic pig on days (d) 0, 2, 4, 7, 9, 11, and 14. *C*: Wound closure rates of the vehicle-, the FN-, the EPO-, and the EPO/FN-treated burn wounds in the diabetic pigs. Representative set of photographic images (*D*) and the corresponding laser Doppler scans (*E*) of a vehicle-, a low-dose EPO-, and a high-dose EPO-treated burn wound in a diabetic pig on days 0, 4, 9, and 14. *F*: Wound closure rates of the vehicle-, the low-dose EPO-, and the high-dose EPO-treated burn wounds in the diabetic pigs. Representative set of photographic images (*G*) and the corresponding laser Doppler scans (*H*) of a vehicle-, an FN-, an EPO-, and an EPO/FN-treated burn wound in a nondiabetic pig on days 0, 4, 9, and 14. The white circles in the laser Doppler scans represent the burn wound area on day 0. The dark blue color represents nonvascularized regions, and the yellow and red colors represent vascularized regions with the red-colored regions depicting regions that are more vascularized than the yellow-colored regions. *I*: Wound closure rates of the vehicle-, FN-, EPO-, and EPO/FN-treated burn wounds in the nondiabetic pigs. The sample size in each treatment group was 12 except in the low-dose EPO-treated burn wound group, where the sample was 6. **P* < 0.05; ***P* < 0.01, significance of the difference between the vehicle-treated burn wounds and the other treatments according to the results of a two-way ANOVA with Bonferroni correction. †*P* < 0.05, significance of the difference between *1*) the EPO-treated or EPO/FN-treated burn wounds and the FN-treated burn wounds and *2*) the high-dose EPO-treated burn wounds and the low-dose EPO-treated burn wounds according to the results of a

Int J Biol Sci. 2014; 10(8): 921–939.
Published online 2014 Aug 23. doi: 10.7150/ijbs.9518
Erythropoietin, a Novel Versatile Player Regulating Energy Metabolism beyond the Erythroid System

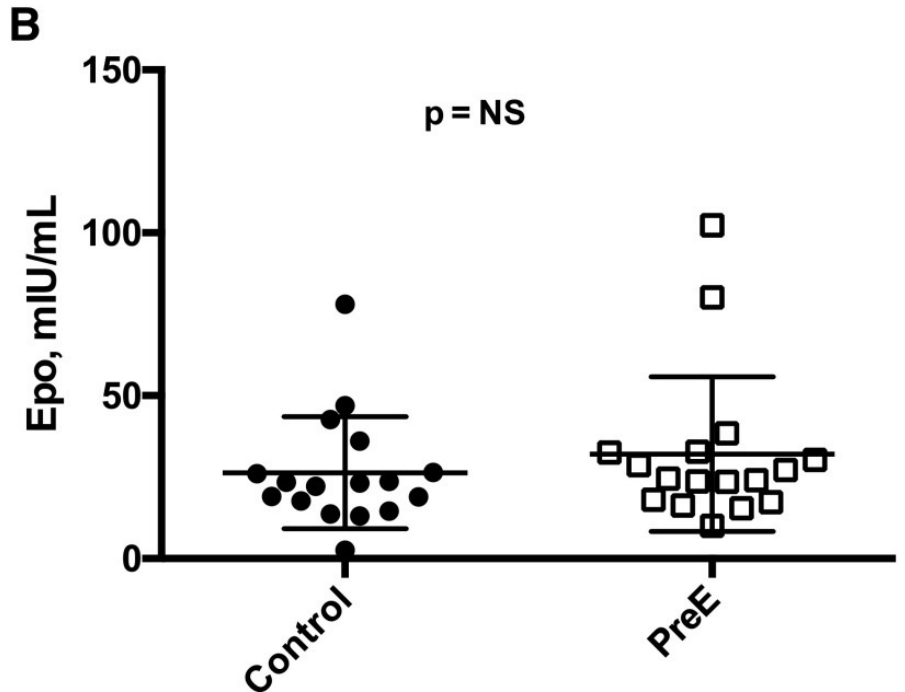
Li Wang,[1,] Lijun Di,[1,] and Constance Tom Noguchi[2]



The pleiotropic activity of EPO in multiple tissues beyond hematopoietic tissues. EpoR expression was detected on erythroid cells, adipocytes, immune system cells such as macrophages, pancreatic beta cells, skeletal muscle myoblasts, neural cells, hypothalamus neurons and endothelial cells. The primary function of the EPO/EpoR system is to stimulate erythroid progenitor cell proliferation, survival and differentiation to provide adequate red blood cells. The well documented non hematopoietic effect of EPO is cytoprotection including cardioprotection and neuroprotection, which are also contributed by the EPO activity in endothelial cells such as angiogenesis. The newly revealed biological activity of EPO includes prevention from obesity and metabolic disorders and improvement of insulin resistance and glucose intolerance. These effects are contributed by EPO promoted energy metabolism in adipocytes, anti-inflammation in macrophages, antiapoptosis in pancreatic beta cells, and the central control of energy intake in hypothalamus neurons.



Matthew



J Clin Endocrinol Metab. 2017 Jan 1;102(1):242-250. doi: 10.1210/jc.2016-1767.

Erythropoietin and Soluble Erythropoietin Receptor: A Role for Maternal Vascular Adaptation to High-Altitude Pregnancy.

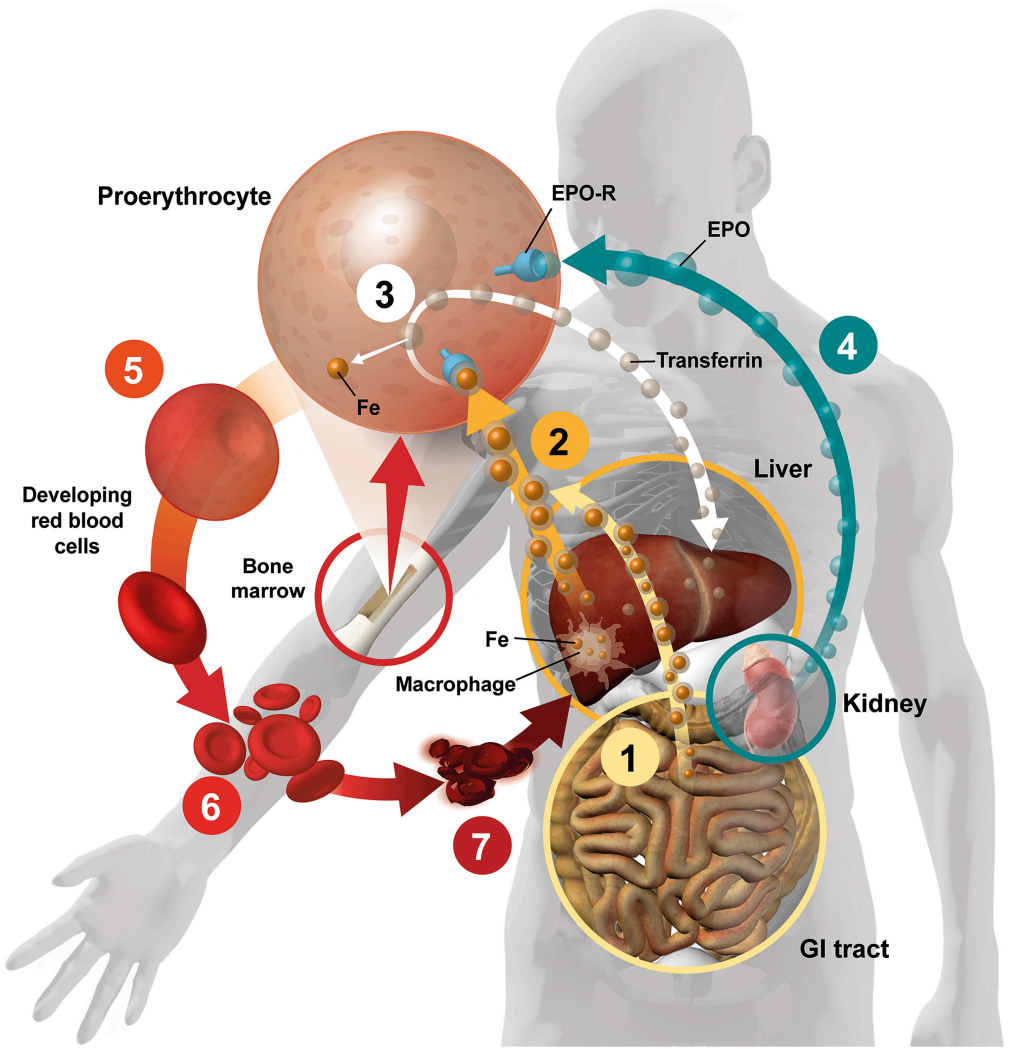
Wolfson GH[1], Vargas E[2], Browne VA[3], Moore LG[4], Julian CG[1].

Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors: A Potential New Treatment for Anemia in Patients With CKD

Nupur Gupta, MD, Jay B. Wish, MD

American Journal of Kidney Diseases
Volume 69 Issue 6 Pages 815-826 (June 2017)
DOI: 10.1053/j.ajkd.2016.12.011

Figure 2



American Journal of Kidney Diseases 2017 69815-826DOI: (10.1053/j.ajkd.2016.12.011)

Effets secondaires traitement Epo

- hypertension
- thromboembolism.
- later tumor metastasis and mortality (

These side effects are related mainly to high-dose chronic EPO treatment, associated with increased hematocrit. Using variants of EPO without hematopoietic effect but retaining tissue protective activity could be useful in a clinical situation in which multiple EPO administrations would be warranted.

Mol Pharmacol. 2014 Jun;85(6):898-908. doi: 10.1124/mol.113.091157. Epub 2014 Apr 2.

Mechanism of erythropoietin regulation by angiotensin II.

Kim YC[1], Mungunsukh O, McCart EA, Roehrich PJ, Yee DK, Day RM.

Author information

Abstract

Erythropoietin (EPO) is the primary regulator of red blood cell development. Although hypoxic regulation of EPO has been extensively studied, the mechanism(s) for basal regulation of EPO are not well understood. In vivo studies in healthy human volunteers and animal models indicated that angiotensin II (Ang II) and angiotensin converting enzyme inhibitors regulated blood EPO levels. In the current study, we found that Ang II induced EPO expression in situ in murine kidney slices and in 786-O kidney cells in culture as determined by reverse transcription polymerase chain reaction. We further investigated the signaling mechanism of Ang II regulation of EPO in 786-O cells. Pharmacological inhibitors of Ang II type 1 receptor (AT1R) and extracellular signal-regulated kinase 1/2 (ERK1/2) suppressed Ang II transcriptional activation of EPO. Inhibitors of AT2R or Src homology 2 domain-containing tyrosine phosphatase had no effect. Coimmunoprecipiation experiments demonstrated that p21Ras was constitutively bound to the AT1R; this association was increased by Ang II but was reduced by the AT1R inhibitor telmisartan. Transmembrane domain (TM) 2 of AT1R is important for G protein-dependent ERK1/2 activation, and mutant D74E in TM2 blocked Ang II activation of ERK1/2. Ang II signaling induced the nuclear translocation of the Egr-1 transcription factor, and overexpression of dominant-negative Egr-1 blocked EPO promoter activation by Ang II. These data identify a novel pathway for basal regulation of EPO via AT1R-mediated Egr-1 activation by p21Ras-mitogen-activated protein kinase/ERK kinase-ERK1/2. Our current data suggest that Ang II, in addition to regulating blood volume and pressure, may be a master regulator of erythropoiesis.

PMID: 24695083 DOI: 10.1124/mol.113.091157

Vitam Horm. 2017;105:57-77. doi: 10.1016/bs.vh.2017.02.001. Epub 2017 Mar 27.

Erythropoietin Regulation by Angiotensin II.

Kim YC[1], Mungunsukh O[1], Day RM[2].

Author information

Abstract

The renin-angiotensin system (RAS) is a key regulator of blood pressure and blood volume homeostasis. The RAS is primarily comprised of the precursor protein angiotensinogen and the two proteases, renin and angiotensin-converting enzyme (ACE). Angiotensin I (Ang I) is derived from angiotensinogen by renin, but appears to have no biological activity. In contrast, angiotensin II (Ang II) that has a variety of biological functions in the cells is converted from Ang I through removal of two-C-terminal residues by ACE. The physiological effects of Ang II are due to Ang II signaling through specific receptor binding, resulting in muscle contraction leading to increased blood pressure and volume. To modulate RAS, three classes of drugs have been developed: (1) renin inhibitors to prevent angiotensinogen conversion to Ang I, (2) ACE inhibitors, to prevent Ang I processing to Ang II and (3) angiotensin receptor blockers, to inhibit Ang II signaling through its receptor. Studies using the RAS inhibitors and Ang II demonstrated that RAS signaling mediates actions of Ang II in the regulation of proliferation and differentiation of specific hematopoietic cell types, especially in the red blood cell lineage. Accumulating evidence indicates that RAS regulates EPO, an essential mediator of red cell production, for human anemia and erythropoiesis in vivo and in vitro. The regulation of EPO expression by Ang II may be responsible for maintaining red blood cell homeostasis. This review highlights the biological roles of RAS for blood cell and EPO homeostasis through Ang II signaling. The molecular mechanism for Ang II-induced EPO production of the cell or tissue type-specific expression is discussed.

KEYWORDS:

Angiotensin II; Egr-1; Erythropoiesis; Erythropoietin; Gene regulation; Kidney; MAPK; Radiation; Ras; Signal transduction

PMID: 28629525 DOI: 10.1016/bs.vh.2017.02.001