Erythropoietin (Epo) regulates hypoxic ventilation by interacting with brainstem and carotid bodies.
Breathing:

Ventilation

Diaphragm

Central nervous system

Brainstem

Peripheral nervous system

Blood

Tissue

Cells

O₂

CO₂
Ventilation under HYPOXIA (diminished PpO₂)

↓PaO₂
Molecules controlling the ventilation:

- Steroids
- Amines
- Neurotransmitters

Hypoxia-activated Molecules (HIF-1)

- target genes
  - Epo

(Pascual, 2004)

(Kline, 2002)
Epo expression occurs in:

- kidney
- liver

but also in other organs including:

- brain
- testis
- lung
3 “anti” roles of Epo:

- anti-apoptotic
- anti-cytotoxic
- anti-oxidative

(Tann et al 1992; Masuda et al. 1993; Morishita et al 1997; Koshimura et al. 1999; Tanaka et al. 2001)
Epo and Epo receptor (EpoR) in brain

- Epo & EpoR are expressed in the mammalian and human brain.
- Cerebral Epo is induced by hypoxia.
- Are expressed by neurons and astrocytes.
Does brain-derived Epo play a role in the control of ventilation under hypoxia?
Transgenic Tg21

- Overexpress Epo **ONLY** in brain (4 x/Wt)
- **NORMAL** Epo in plasma; HB ; Hct
Tg21 maintain high ventilation under at 6% hypoxia

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Tg21 enhance ventilation after chronic hypoxia

- hypoxic chamber
- 3 days at 10% O₂
**EpoR** is expressed in the resp. areas of the brainstem

**Legends:**

4V, 4th ventricle; AP, area postrema; NTS, nucleus tractus solitarius; 7n, facial nerve; PBC, Pre-Bötzinguer complex; NA, nucleus ambiguus; PY, pyramidal decussation; LC, locus ceruleus. Catecholaminergic areas in the medulla oblongata: A1C1 & A2C2 and in the pons: A5 & A6

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Chemodenervation is **life-threatening in Wt** but not in Tg21
Is the Epo impact on ventilation a neuro-protective phenomenon?
Are Catecholamines involved in the impact of Epo in ventilation?
Catecholaminergic group cells in the brainstem
A2C2 cell group

Noradrenaline pmoles/20min

TH activity

NE content

pmoles DOPA/20min

pmoles NE
does plasma-derived Epo impact hypoxic ventilation via CB?
EpoR is expressed in Carotid bodies glomic cells

Legends:
TH, tyrosine hydroxilase; Epo-R, erythropoietin receptor; ICA, internal carotid artery; ECA, external carotid artery; CCA, commun carotid artery
**Epo injected (i.v.) in Wt mice** modulates the hypoxic ventilatory pattern

Injection of Epo (iv)

(2000 U/Kg: 50 U/mouse)

Epo does not cross the BBB

VE = RR x VT

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**VE (m/min/100g)**

- NaCl-inj
- Epo-inj

**RR (resp/min)**

**VT (mL/100g)**
Carotid body slices: *Wistar* rats (2 wk old)

Spain: Lopez-Barneo

Epo triplicates the CB evoked response under hypoxia

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Conclusion

- Brain-derived Epo (via EpoR in brainstem) and systemic Epo (via EpoR in carotid bodies) modulate ventilation under hypoxia

- These results suggest that Epo has crucial role in the fine-tuning of oxygen homeostasis

High altitude dwellers?
Acute and Chronic mountain sickness?
Lance Amstrong ...Epo doping?
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Is the Epo effect on ventilation a selective action?

Epo mediates general integrity to the tissue.
Hello, hello,.... how much oxygen do you have over there?