Don’t Hold Your Breath

Mammalian Adaptations to High Altitudes

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BSCI 440

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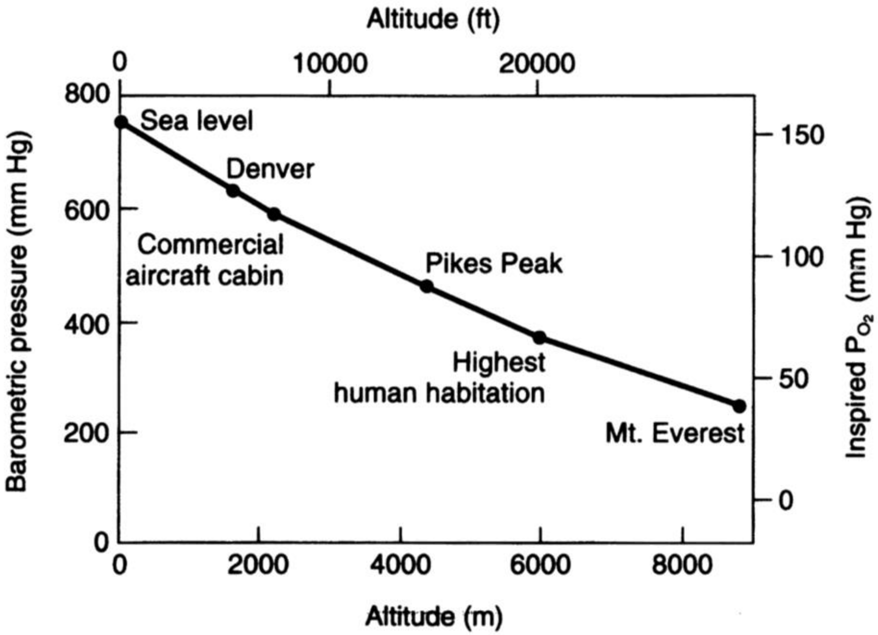
Outline

- What can go wrong: acute mountain sickness, HAPE, & HACE
- Human adaptations: Tibetans & Andeans
- Animal adaptations: yaks vs. cattle

High Altitude Humans

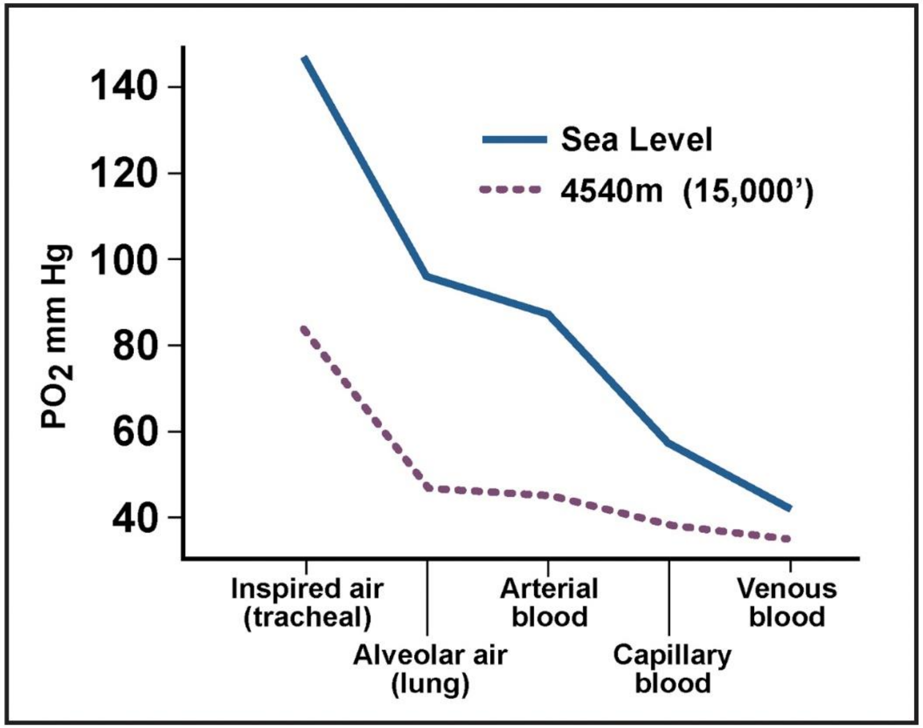
Atmospheric Gases

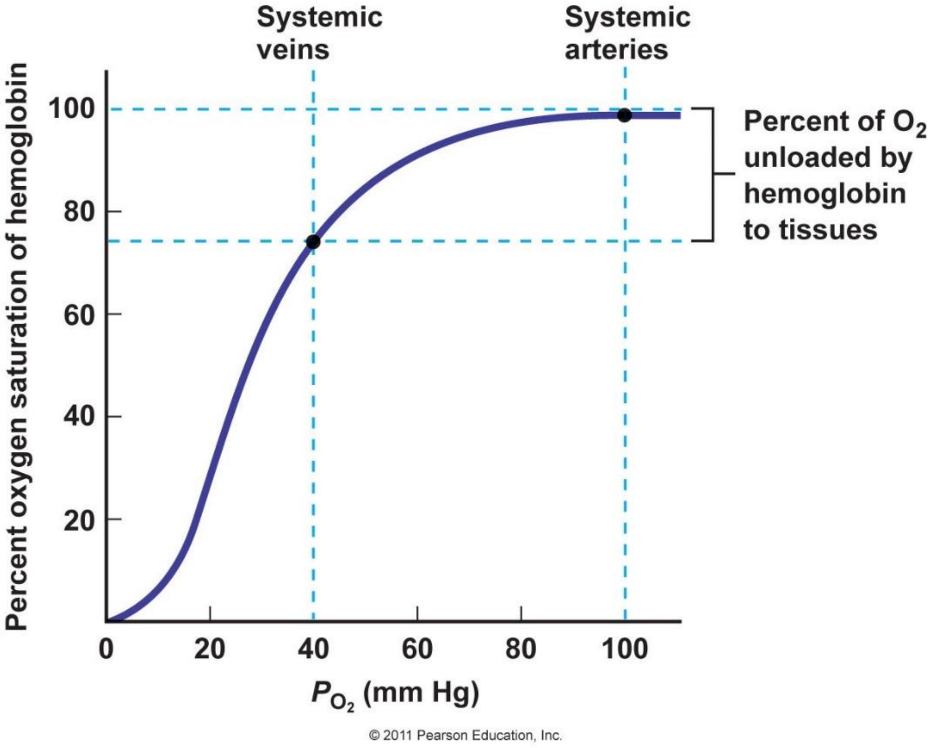


Dalton's Law: $P_t = P_{O2} + P_{N2} + P_x$

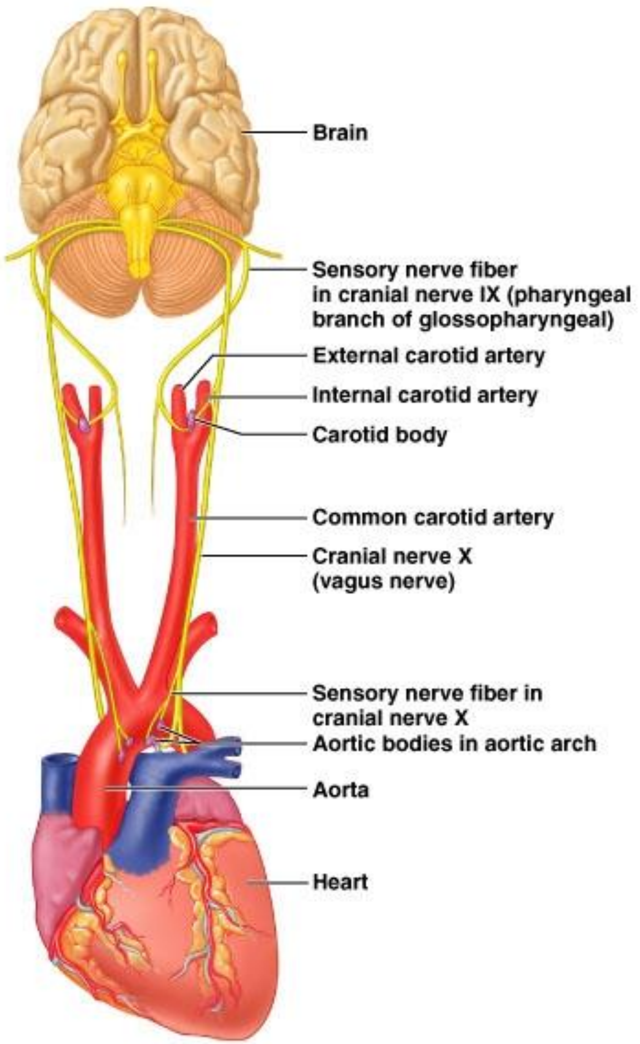
Altitude (feet)	Atmospheric Pressure (mm/Hg)	PAO_2 (mm/ Hg)	PVO_2 (mm/ Hg)	Pressure Differential (mm/Hg)	Blood Saturation (%)
Sea Level	760	100	40	60	98
10,000	523	60	31	29	87
18,000	380	38	26	12	72
22,000	321	30	22	8	60
25,000	282	7	4	3	9
35,000	179	0	0	0	0

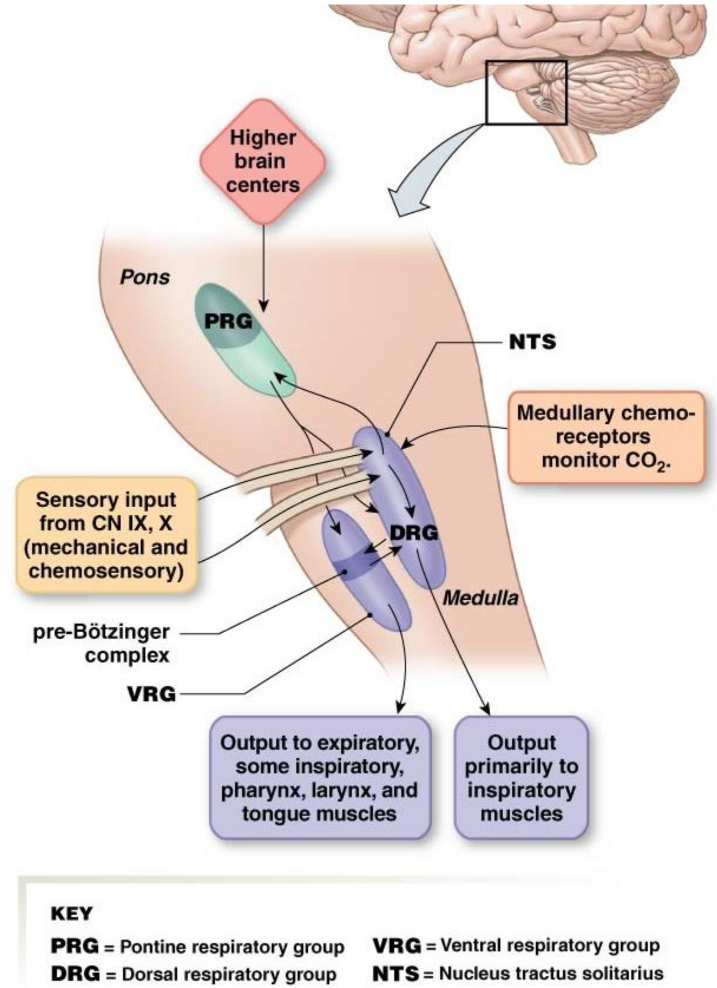
Partial Pressure of Oxygen





Carotid Body and Medulla





Acute Mountain Sickness: fatigue, nausea, dizziness, headache, rapid pulse, dyspnea

- Hypoxemia, hypocapnia, & alkalosis
- Acetazolamide for prophylaxis ? Why?
- Caused by decreased ventilation drive & erythrocytosis
  - people with AMS have lower minute ventilation, higher expired CO_2, & lower arterial O_2
  - Hb > 200 g/L, Hct > 65%, and arterial O_2 < 85%
  - Maximum oxygen intake decreases 20-30%

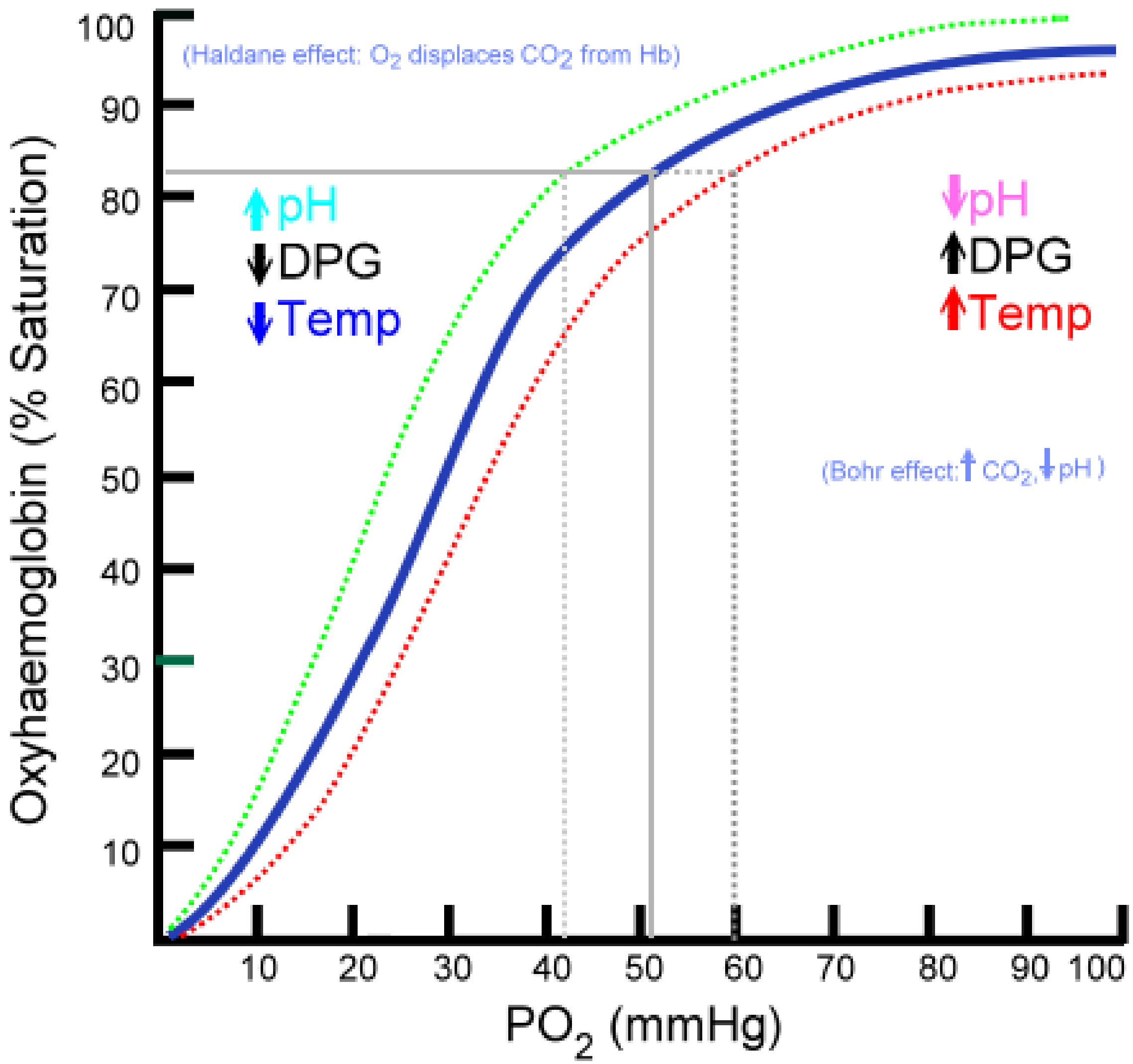
Acclimatization

- ↑Erythropoietin → ↑hematocrit and hemoglobin
  - at high enough concentrations, can increase blood viscosity enough to compromise vasculature & decrease tissue oxygenation
- ↑2,3-DPG

?

Why would this help?

Hemoglobin



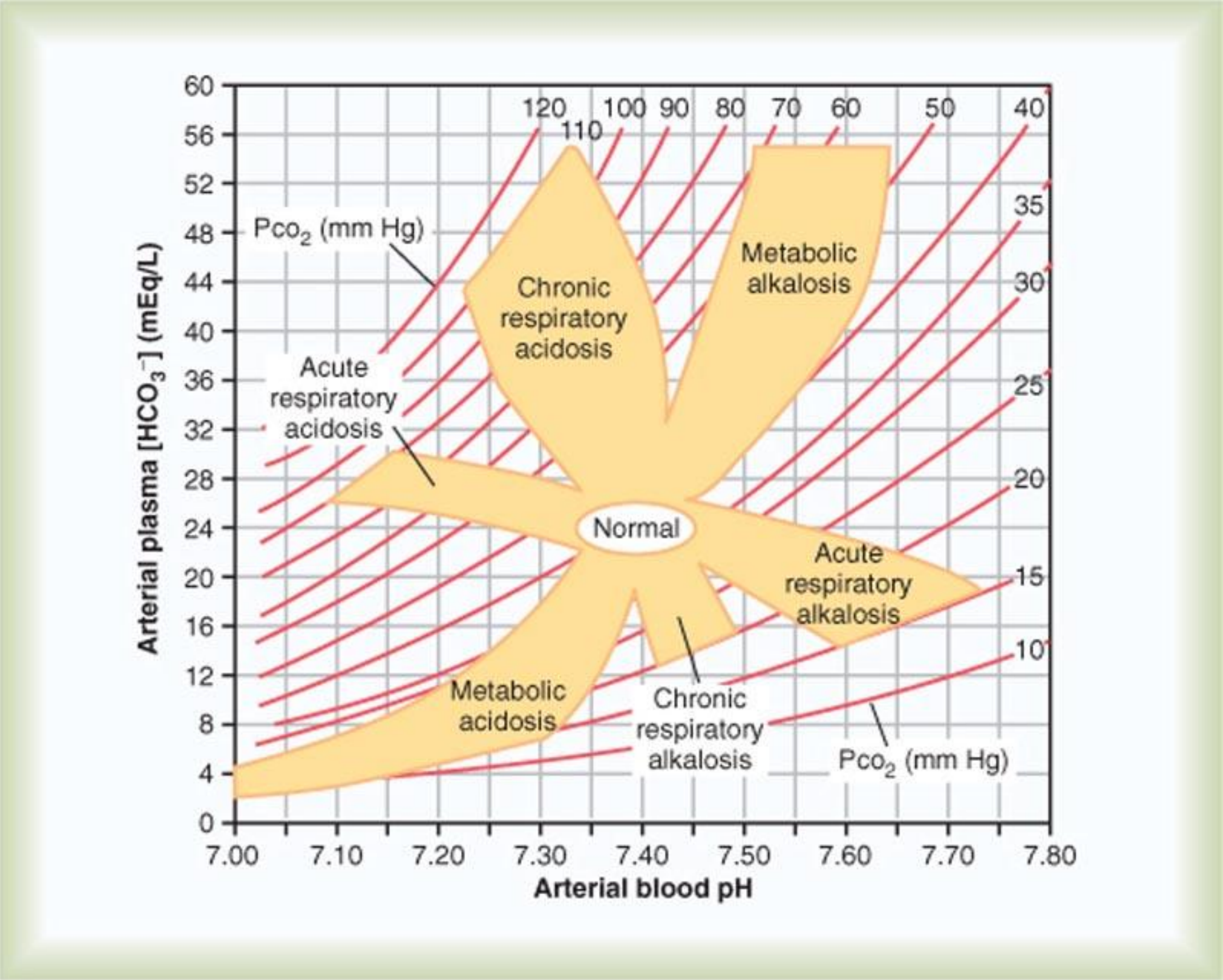
(Haldane effect: O_2 displaces CO_2 from Hb)
↑pH
↓DPG
↓Temp
↓pH
↑DPG
↑Temp
(Bohr effect: ↑ CO_2, ↓pH)
Oxyhaemoglobin (% Saturation)
100
90
80
70
60
50
40
30
20
10
10 20 30 40 50 60 70 80 90 100
PO_2 (mmHg)

Acclimatization

- ↑Erythropoietin → ↑hematocrit and hemoglobin
  - at high enough concentrations, can increase blood viscosity enough to compromise vasculature & decrease tissue oxygenation
- ↑2,3-DPG
- ↑renal excretion of bicarbonate

? Why would this help?

Renal compensation for respiratory alkalosis: excrete bicarbonate



Acclimatization

- ↑Erythropoietin → ↑hematocrit and hemoglobin
  - at high enough concentrations, can increase blood viscosity enough to compromise vasculature & decrease tissue oxygenation
- ↑2,3-DPG
- ↑renal retention of bicarbonate
- Maximum oxygen intake increases to nearly normal levels over 1 year
- Proposed mechanism: ↑ carotid chemoreceptor activity

High Altitude Cerebral & Pulmonary Edema (HACE/HAPE)

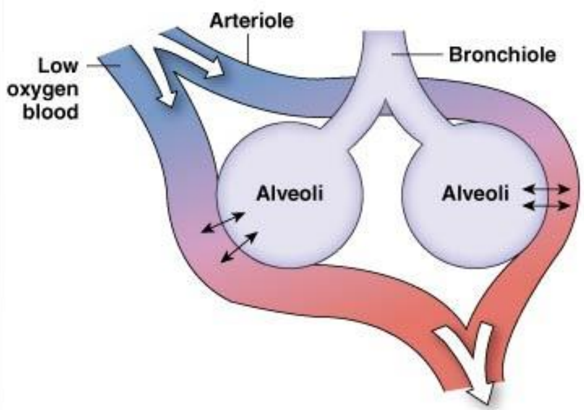
- Symptoms: confusion, decreased consciousness, grey complexion, coughing
- Pulmonary edema from vaso
- Cerebral edema from vaso
- Treat with anti-inflammatory & phosphodiesterase inhibitor (reduces pulmonary artery pressure)

? Why?

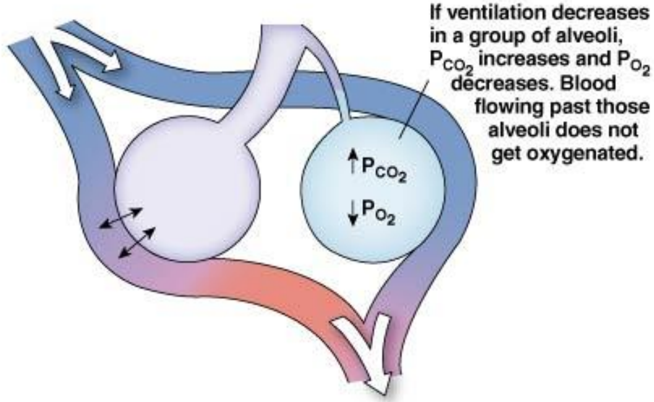
Pulmonary Vasoconstriction

Local control mechanisms attempt to match ventilation and perfusion.

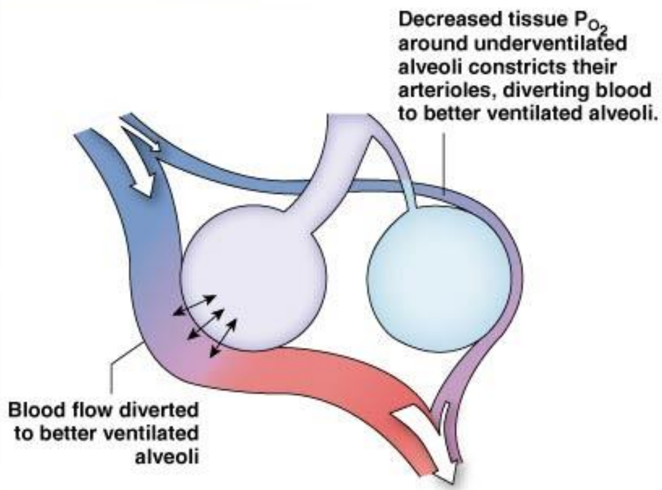
(a) Normally perfusion of blood past alveoli is matched to alveolar ventilation to maximize gas exchange.



(b) Ventilation-perfusion mismatch caused by under-ventilated alveoli.



(c) Local control mechanisms try to keep ventilation and perfusion matched.



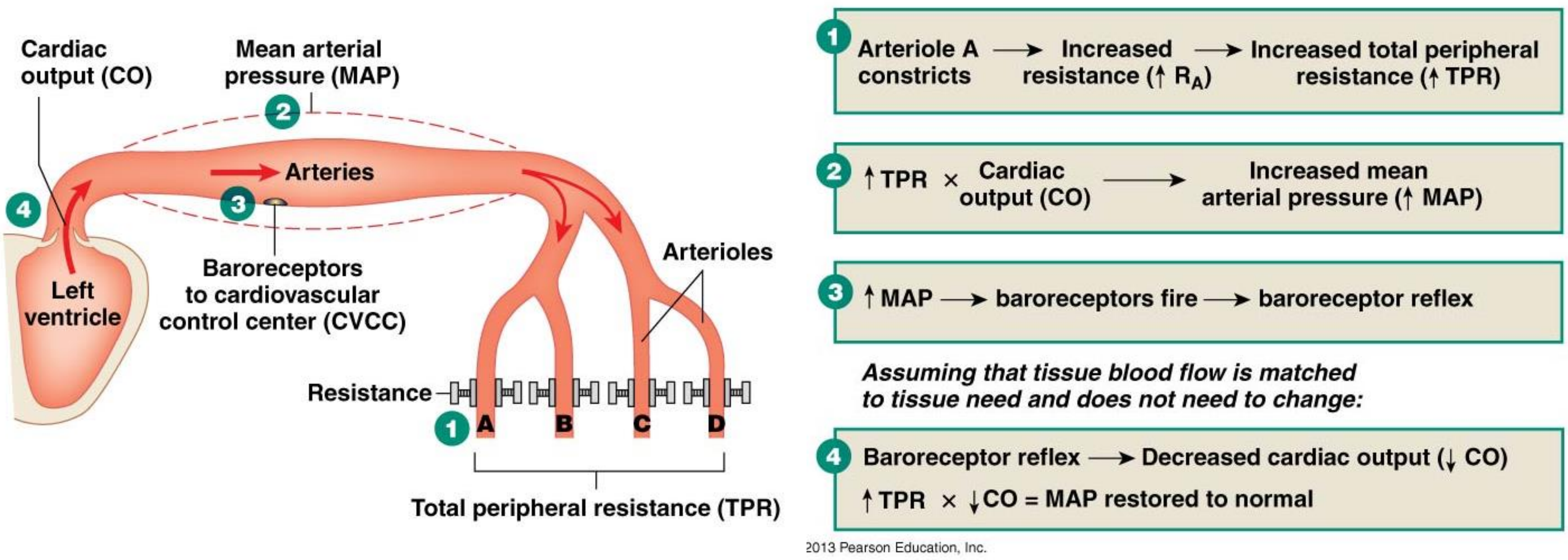
(d) Bronchiole diameter is mediated primarily by CO_2 levels in exhaled air passing through them.

Local Control of Arterioles and Bronchioles by Oxygen and Carbon Dioxide

Gas composition	Bronchioles	Pulmonary arteries	Systemic arteries
P_{CO_2} increases	Dilate	(Constrict)*	Dilate
P_{CO_2} decreases	Constrict	(Dilate)	Constrict
P_{O_2} increases	(Constrict)	(Dilate)	Constrict
P_{O_2} decreases	(Dilate)	Constrict	Dilate

* Parentheses indicate weak responses.

CO = MAP/TPR



Cardiac output (CO)
Mean arterial pressure (MAP)
2
Arteries
4
3
Left ventricle
Baroreceptors to cardiovascular control center (CVCC)
Arterioles
Resistance
1
A
B
C
D
Total peripheral resistance (TPR)
1 Arteriole A constricts → Increased resistance (↑ R_A) → Increased total peripheral resistance (↑ TPR)
2 ↑ TPR × Cardiac output (CO) → Increased mean arterial pressure (↑ MAP)
3 ↑ MAP → baroreceptors fire → baroreceptor reflex
Assuming that tissue blood flow is matched to tissue need and does not need to change:
4 Baroreceptor reflex → Decreased cardiac output (↓ CO)
↑ TPR × ↓CO = MAP restored to normal
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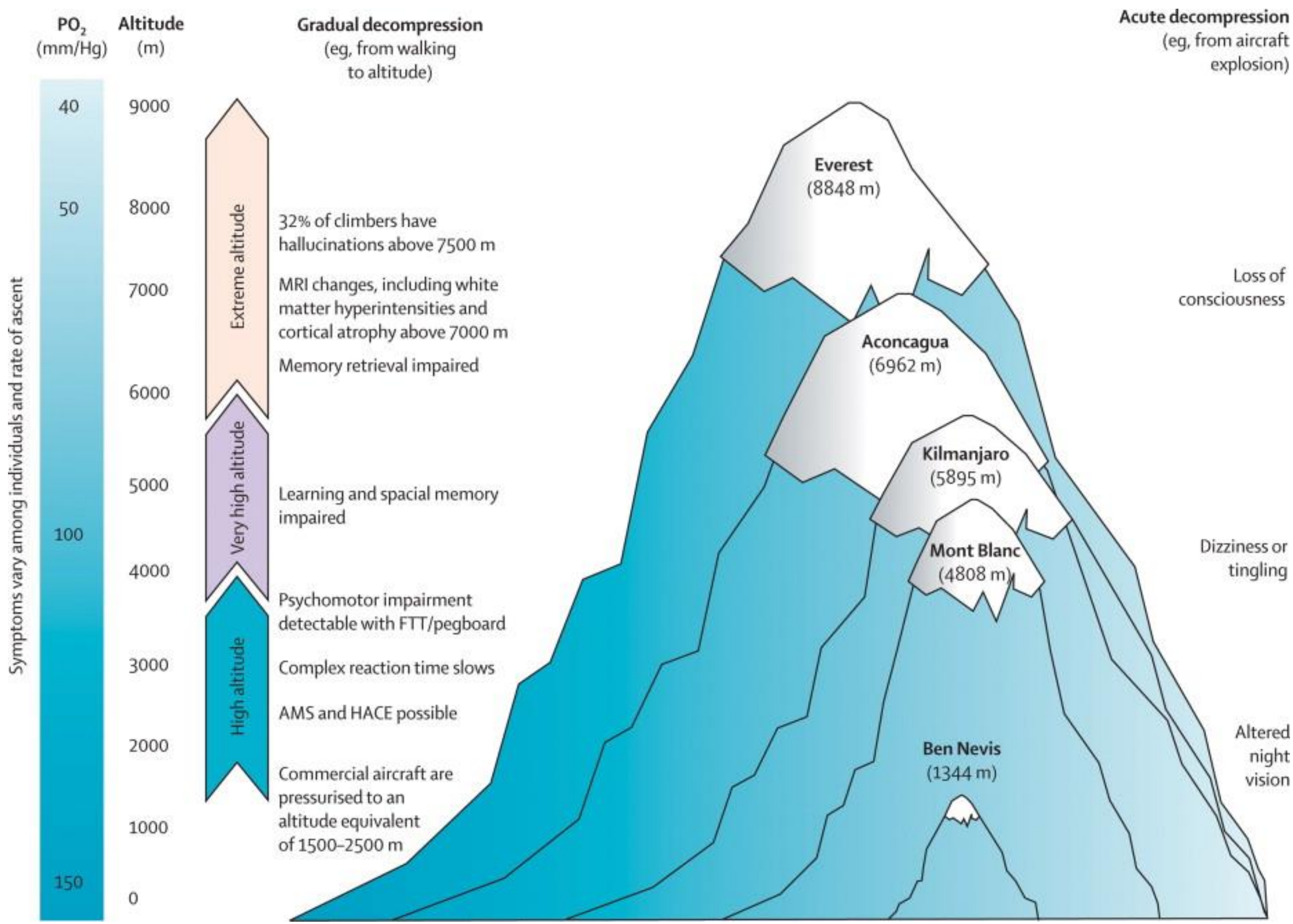
Comparing altitudes: HACE effects



Andeans & Tibetans

Populated since 11,00 years ago
Average elevation: 4000m (13,000ft)

Populated since 25,000 years ago
Average elevation: 4900m (16,000ft)

Highlanders

- Denser capillary beds
- Higher 2,3-DPG
- Exercise capacity is better than lowlanders at high elevation, but not as good as lowlanders at sea level
- Limits: no human habitation above 6000m

? Why would this help?

Andeans & Tibetans

- Andeans have higher [Hb] than lowlanders at sea level
- Tibetans have a higher ventilation rate (15 L/min vs 10.5 L/min)
- Tibetans have increased NO

?

Why would this help?

- Both have heavier babies than expected due to increased NO (Tibetans) and increased gestational ventilation (Andeans), but also have high rates of diseases associated with low fetal oxygen (schizophrenia & epilepsy)
- Overall, Andeans have higher arterial O_2

High Altitude Animals: Yaks vs. Cattle

Varying altitude

- Switch conditions
- Brisket Disease
  - Right side heart failure
  - Pulmonary hypertension

? What is different in Yaks?

Yaks

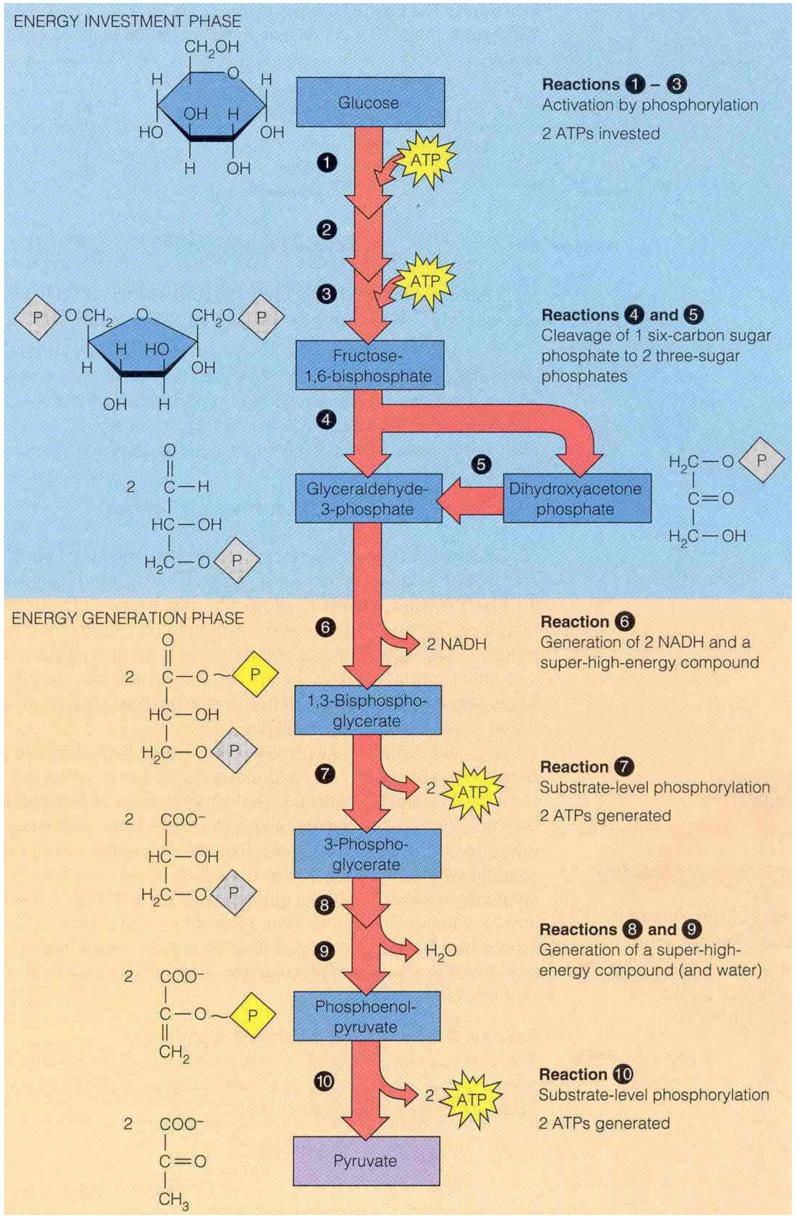
- Hypoxic response is reduced in yaks vs cattle

? Why?

- Larger heart
- Large lungs
- Large chest

Cellular Response

- Glycolysis
- Shift processes
- Necrosis



Genetic response

- VEGF
- NO
- Erythropoietin

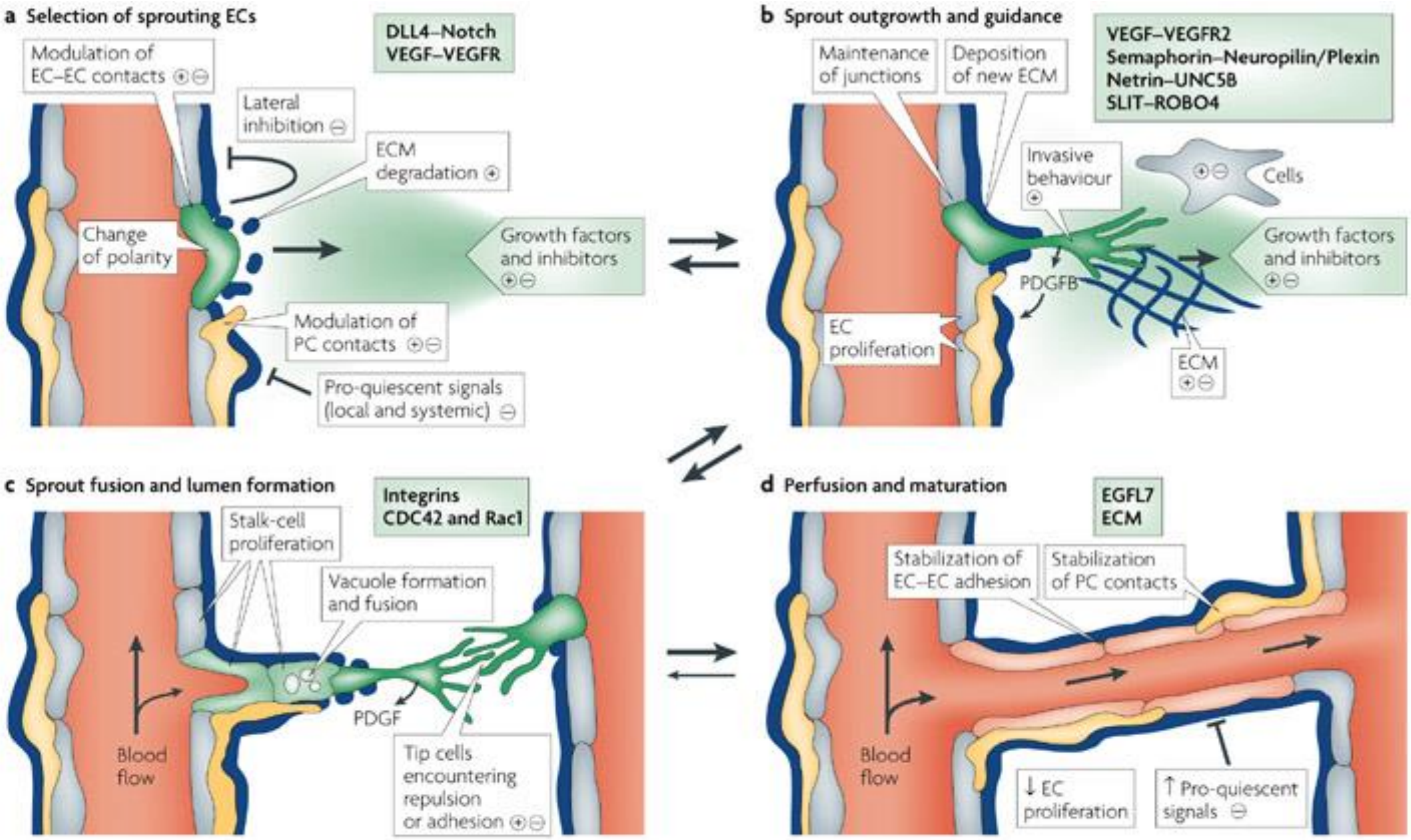
HIF-1

- Hypoxia-inducing factor 1
- Produced in normoxia and hypoxia
  - Normoxia: polyubiquitinylated
  - Hydroxylase destroys HIF-α in presence of O_2
- Stimulates:
  - VEGF
  - Erythropoietin

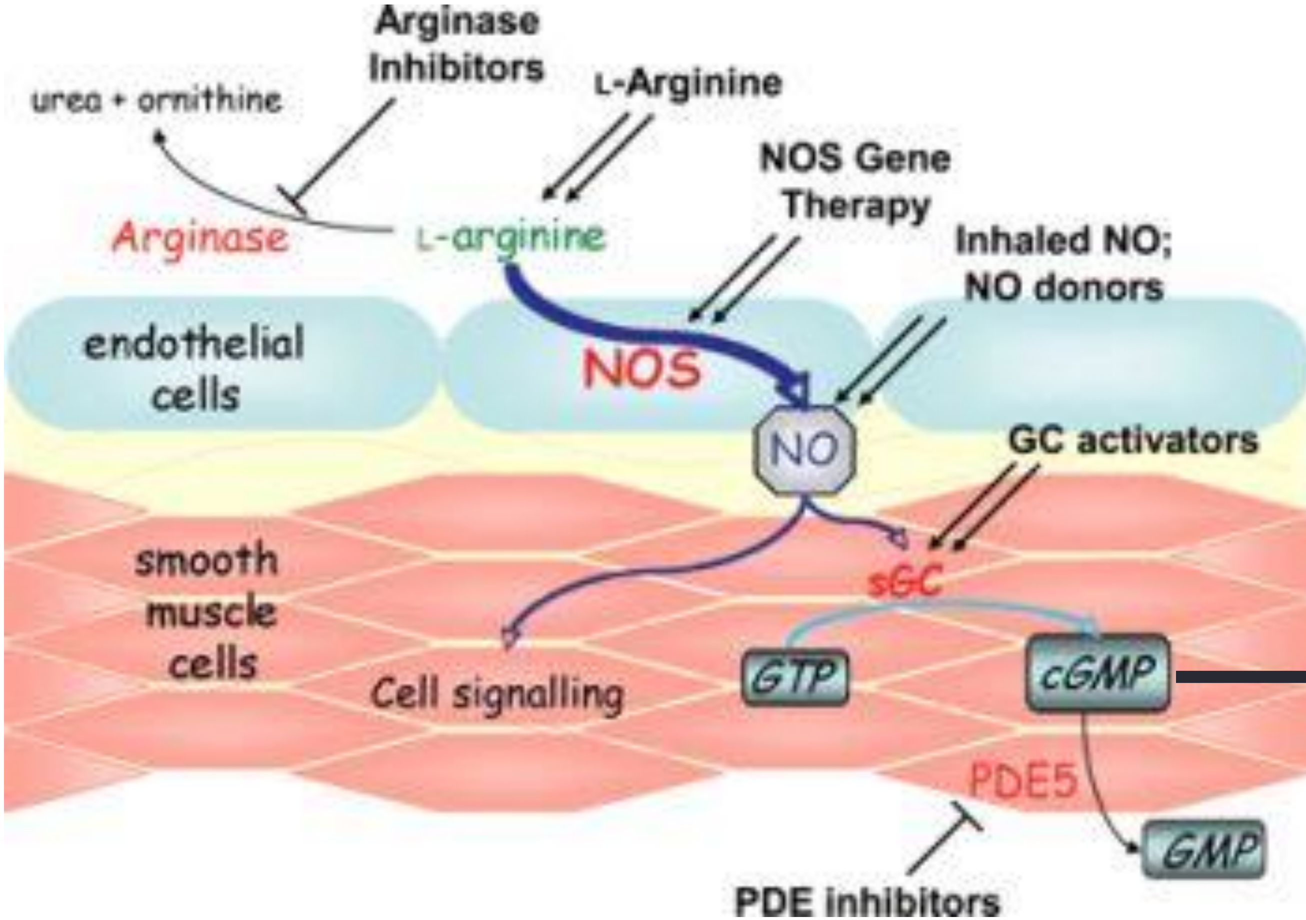
VEGF

- Vascular Endothelial Growth Factor
- Angiogenesis
- NO synthesis

Angiogenesis



NO



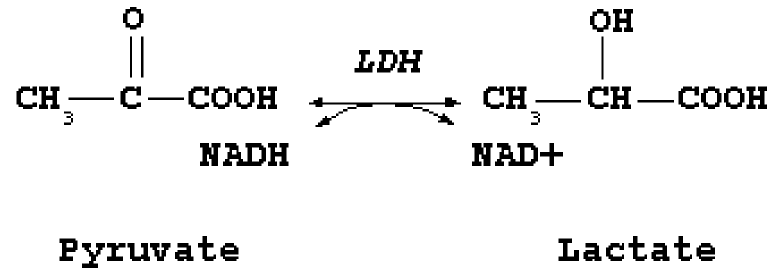
Arginase Inhibitors
urea + ornithine
L-Arginine
NOS Gene Therapy
Arginase
L-arginine
Inhaled NO; NO donors
endothelial cells
NOS
NO
GC activators
smooth muscle cells
sGC
Cell signalling
GTP
cGMP
PDE5
GMP
PDE inhibitors

?
How?

Erythropoietin

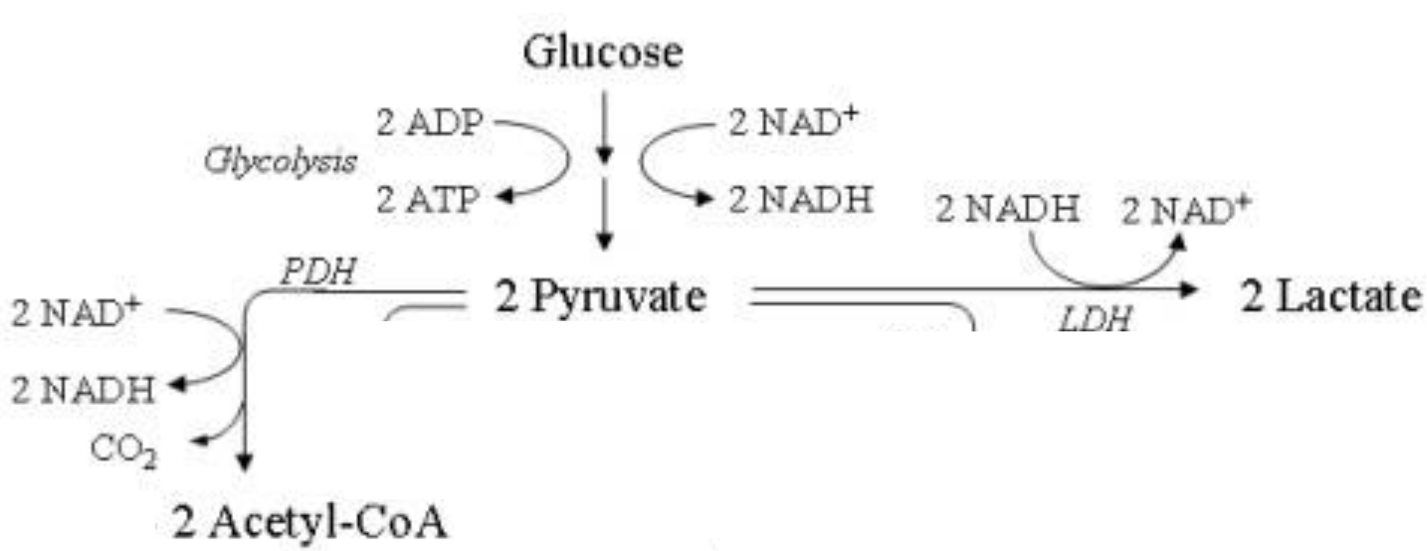
- Released by kidney under hypoxic conditions
- Bone marrow
- Increases red blood cell count

LDH-1



- Lactate dehydrogenase
- Pyruvate → Lactate
- LDH-1 variant with higher Km value

? Why?



Recap

- Morphology (physical structures)
- Sensitivity
- Genetic