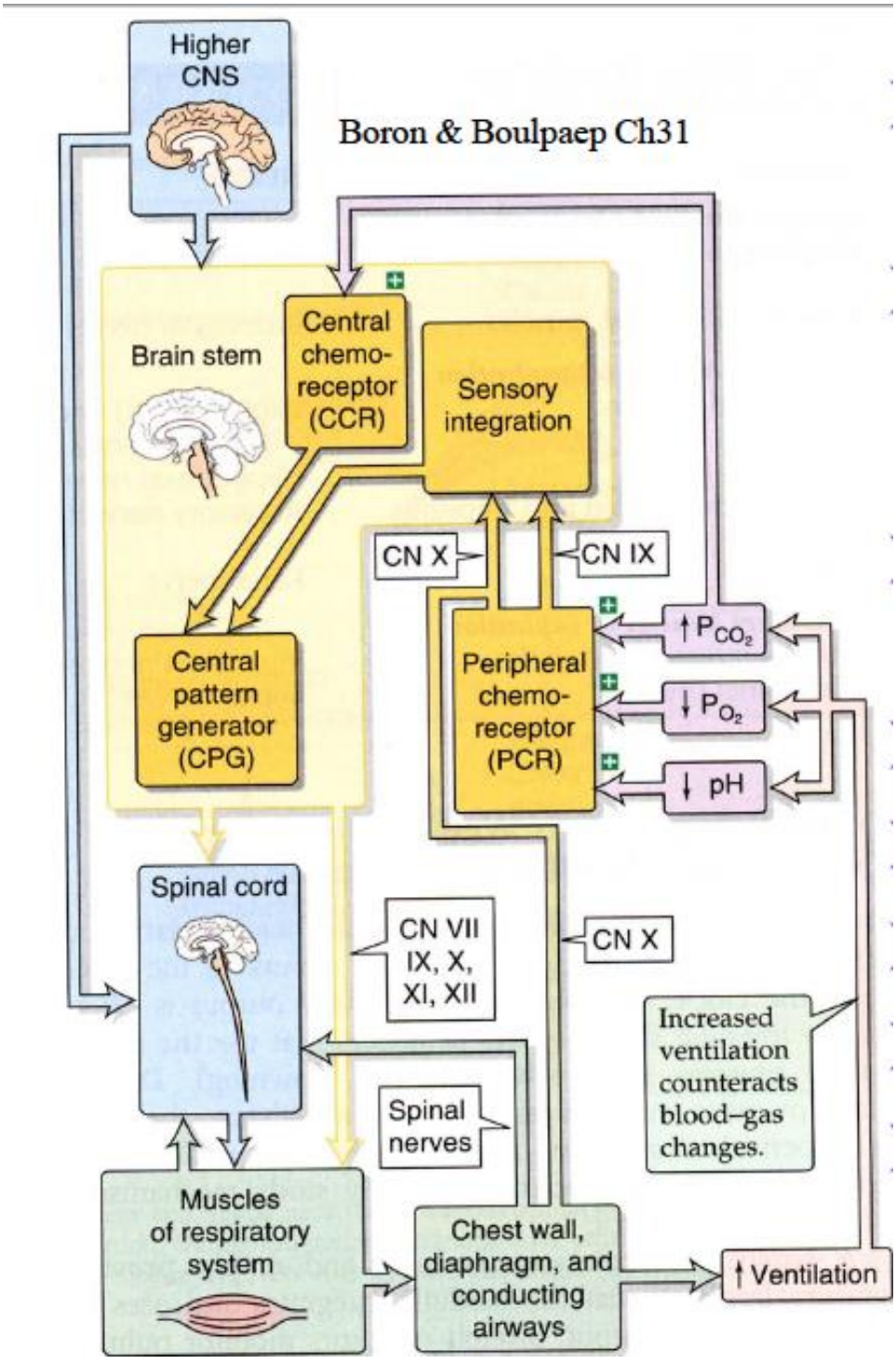
Lecture 3 – Control of Ventilation - McFawn



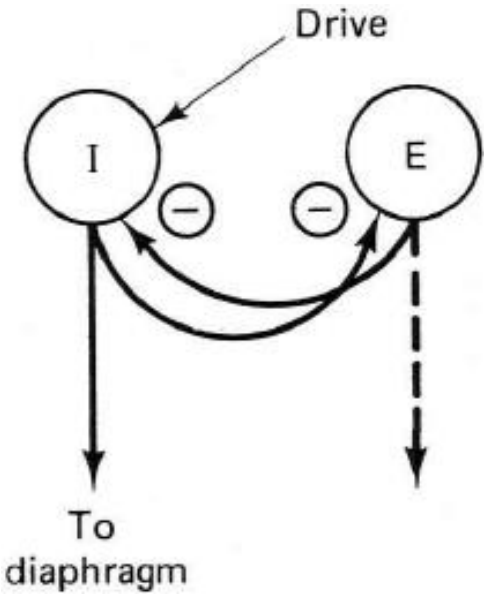
O_2 only affects PCR, CO_2 affects PCR AND CCR

Rhythmogenesis (within medulla oblongata)

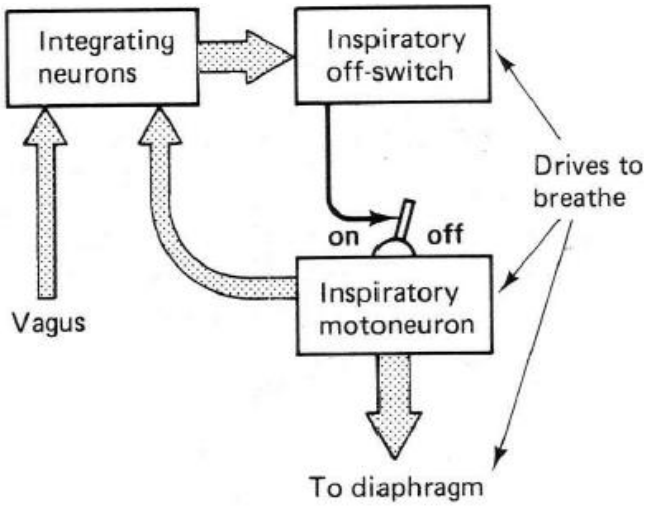
- Sever between medulla and spinal cord stops respiration
- 2 centres
    - Dorsal Respiratory Group: Nucleus tractus solitarius (NTS)

        - Receives afferent input
        - Inspiratory cells to Phrenic nerve
        - Contains cells active in inspiration
    - Ventral Respiratory Group: Nucleus Amiguus (NA), Nucleus Paraambiguus, Nucleus Retroambiguus (NRA)
        - Output to
            - Accessory muscles
            - Expiratory motorneurons
            - Upper airway (NA)
            - Through Vagus to ASM (NA)
        - Cells mostly active in expiration, some active in inspiration, some active in expiration
- Division is not clear –all cells in NA/NRA are respiratory, but not all expiratory cells are in NA/NRA

Rhythm generator models
- Oscillator – NOT TRUE
- Off-switch – POSSIBLE
- Pacemaker Kernel – MOST- LIKELY



Oscillator
- Insp turns on, sends inhibitory feedback to Exp, turns Exp off
- Inhib feedback from Exp turns off Insp, removes -ve feedback on Exp -> Exp turns on
- Exp being on sends inhib to Insp, Insp sends -ve to Exp etc….
- Why is it not true?
    - Inspiratory and expiratory centres are spontaneously active, would mean constant inhibition which ruins the model.



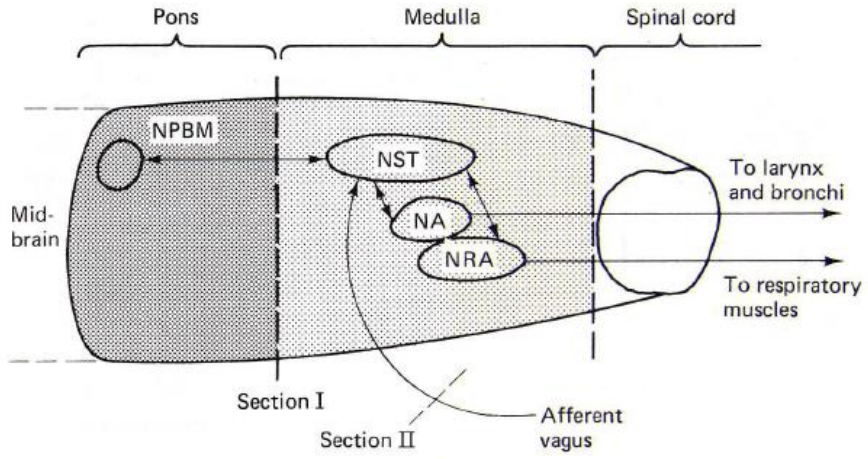
Off-Switch
- Inspiratory motor neuron active -> diaphragm contracts
    - Also sends action potential which go around brain stem (time delay) -> back on itself so it turns off (self-regulating)
- Stays off until no more action potential is circulating, turns on
    - In turning on, contracts diaphragm and also sends action potential to turn itself off

Pacemaker Kernel

- Pre-botzinger neurons exhibit pacemaker like behaviour
  - Hard to study – dissection = damages function
  - Luckily, some glossopharyngeal nerve remains, known to fire in time with respiration
- AP opens Ca_v allowing Ca^{2+} imaging
  - All pacemaker cells act together
  - Glutamate inhibitors block synchrony and respiratory rhythm

Central modification

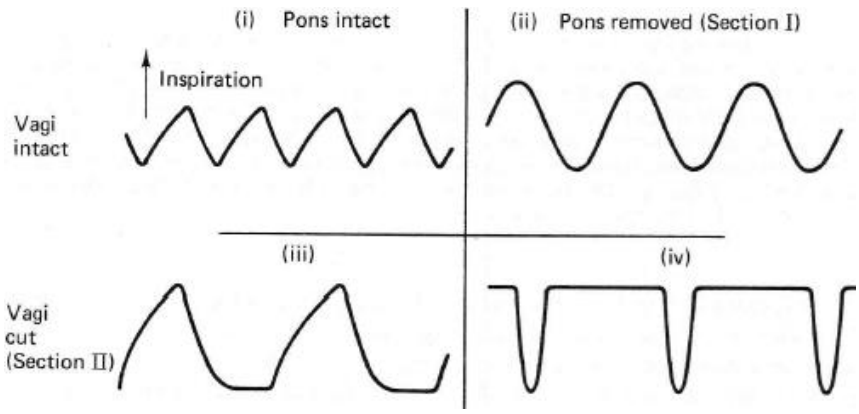
- Isolated medulla generates a respiratory rhythm, but not a normal pattern
- Pnuemotaxic center in Pons shorten inspiration



NPBM: Nucleus parabrachialis medialis

Central control of breathing

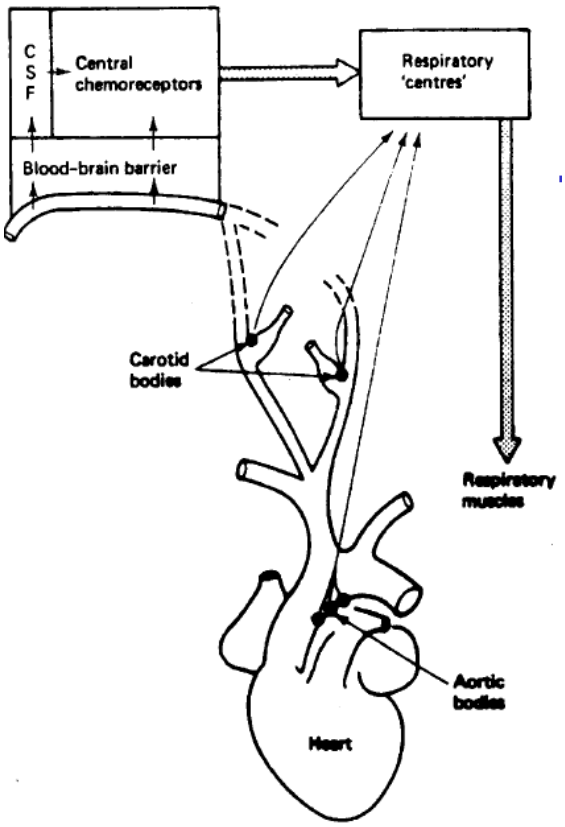
- Respiratory rhythm generated in medulla
- Pons modulates rhythm by inhibiting inspiratory drive (pneumotaxic centre)
- Phrenic nerve to diaphragm arises from cervical cord (C2-C5)
- DRG receives input from Vagus and drives Phrenic
- VRG
  - NA drives vagal efferents to bronchi and glossopharyngeal to larynx
  - NRA drives nerves to intercostal + abdominal muscles



Apnoea: No breathing
Hypernea: Increased ventilation
Hyponea: Decreased ventilation
Hyperventilation: Metabolically inappropriate ventilation increase, causing low CO_2 (alkalosis)
Apneusis: Prolonged inspiration with short expiration
Gasping: Prolong expiration

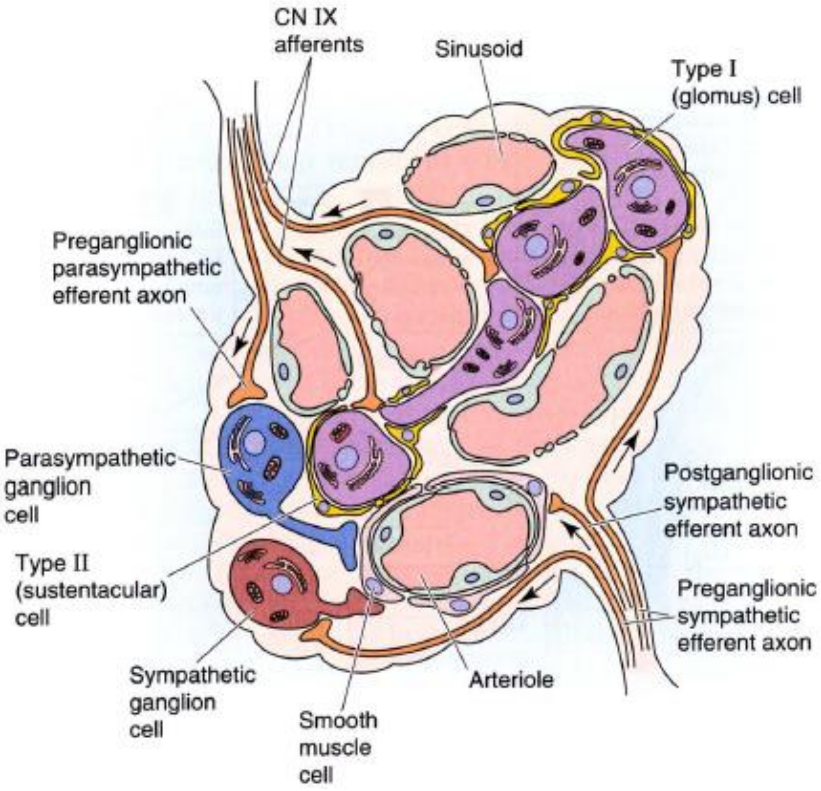
Central Chemoreceptors (CCR)

- CO_2 provides H^+ stimulus
- Located on ventral surface of medulla
- Respond to pH of cerebrospinal fluid (CSF)
    - CSF poorly buffered so it must be protected from changes in blood pH – blood brain barrier does this
    - CO_2 only thing that crosses BBB, causes changes in pH
- Many neuron in CNS respond to pH changes
    - Many cells on ventral surface of medulla respond to pH
        - So do cells in VRG, DRG, Pons and hypothalamus
        - Might be redundant systems?



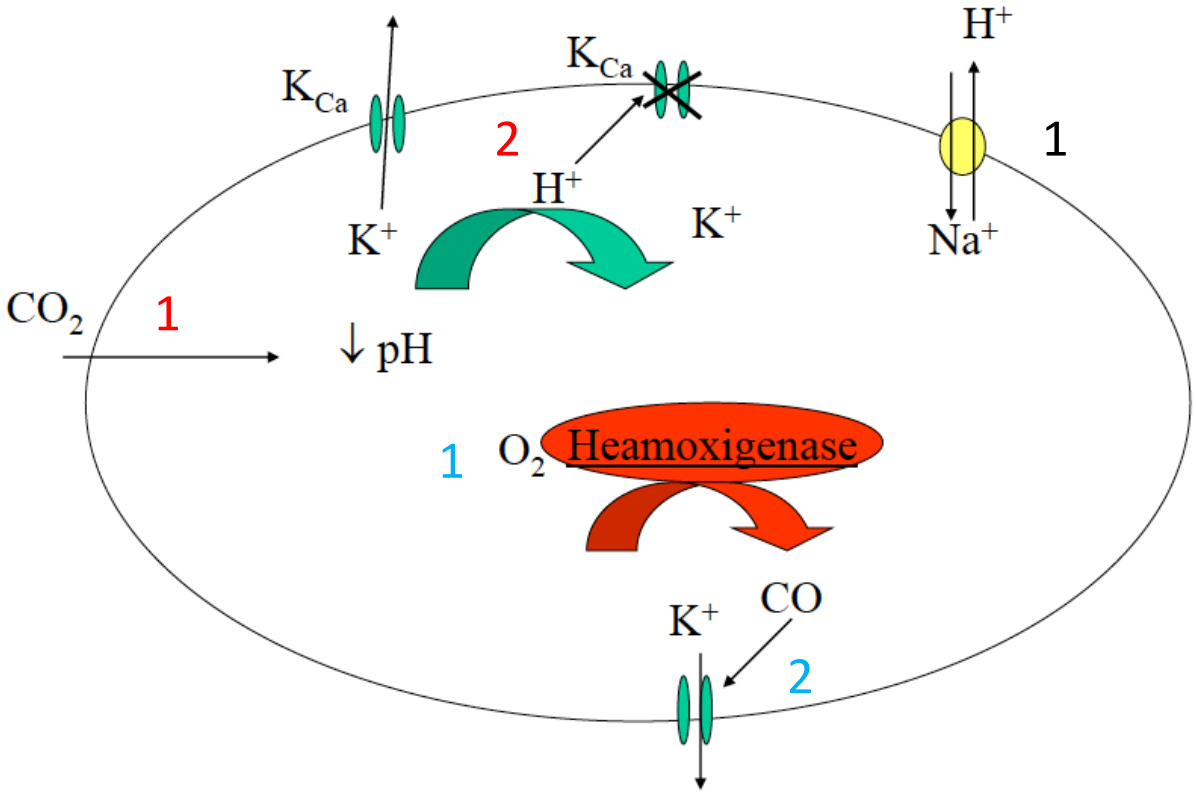
Peripheral Chemoreceptors (PCR)

- Carotid Body: IX cranial nerve – CO_2, O_2 and H^+
- High blood flow
    - None of their metabolic O_2 comes from Hb, all from dissolved O_2
- Aortic body: X cranial – CO_2 and O_2
- Hypoxemia (low O_2) stimulates ventilation
    - Also increases vasotone + HR (increase blood flow)



PCR Anatomy

- Glomus detects O_2, CO_2, pH
    - Neuronal in origin, excitable -> causes neurotransmitter release
- Detect intracellular pH by protonation of K_{Ca} channels
    - Decrease K^+ efflux
    - Hypopolarization -> AP generation
- CO_2 and arterial pH change intracellular pH



PCR responds to changes in CO_2, O_2 and H^+, firing of PCR would increase ventilation

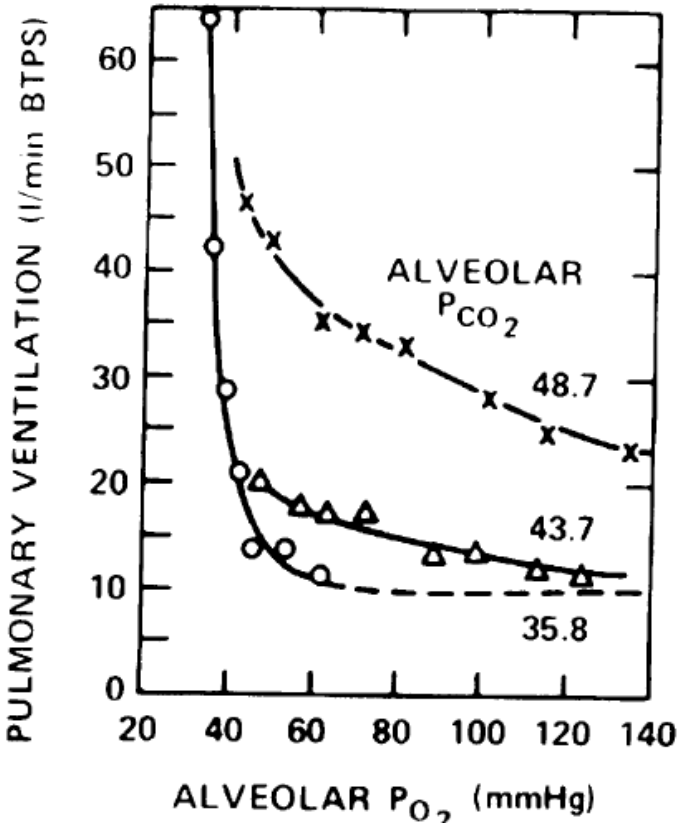
1. CO_2 into the cell, decreases pH (more H^+)
2. H^+ protonates K_{Ca}, reduced K^+ efflux -> more likely to fire

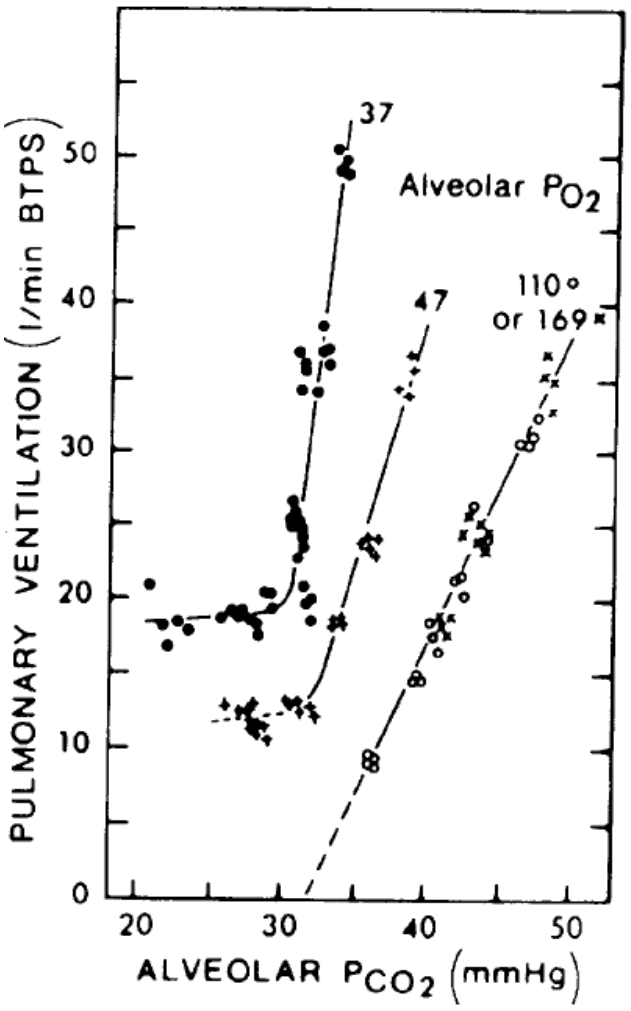
1. O_2 diffuses into cell, haemoxigenase converts to CO
2. CO opens K^+ efflux, keeping cell away from depolarization, conversely, low O_2 would stop the opening on K^+ efflux, K^+ build up -> AP generated

1. If arterial H^+ is high (low pH), Na-H antiport stops, H^+ accumulates in the cell, AP is generated. If arterial H^+ is low (indicative of low CO_2), more H^+ leaves and cell is less likely to fire

Ventilatory response to O_2

- Large increase seen at P_{O2} <60mmHg
- Ventilation enhanced at a given P_{O2} by increase P_{CO2}





Ventilatory response to carbon dioxide

- CCR and PCR
- CCR stimulated by H^+
  - H^+ increased due to increased CO_2
  - Slower than PCR
  - Responsible for 60-80% of increased ventilation
- PCR stimulated by CO_2 and O_2
  - Responsible for 20-40% of increase ventilation
  - Response to P_{CO2} lessened by increased P_{O2}
- Response to CO_2 major driver for ventilation increase in normal people, but what about people with asthma/COPD??(to come)