CO_2 Effects in Space

Relationship to Intracranial Hypertension

CO_2 Effects Terrestrially

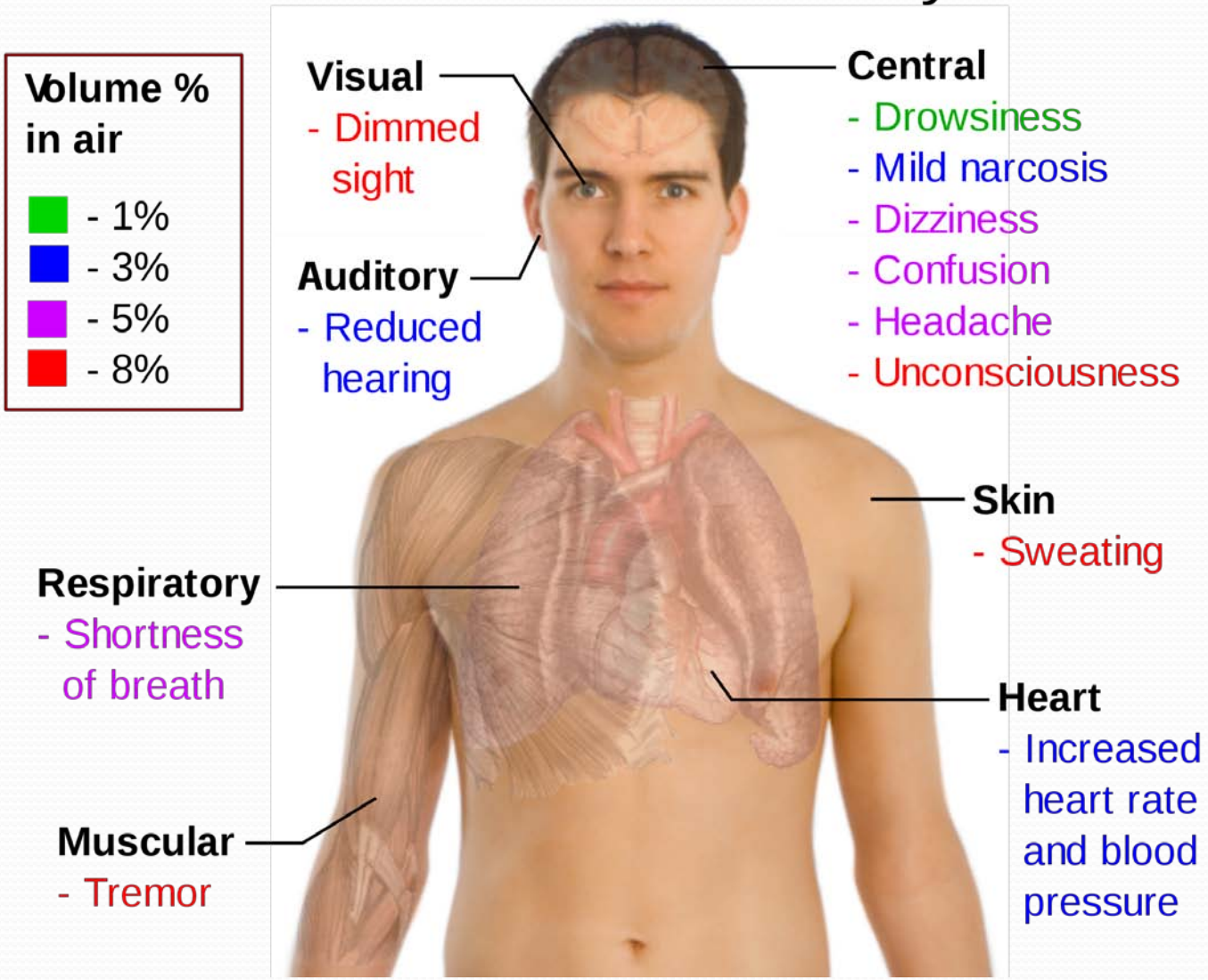
- Terrestrial atmospheric CO_2 level is 0.039% (0.30 mmHg)
- Above **2%** (**15.2 mmHg, 20,000 ppm**), carbon dioxide may cause a feeling of heaviness in the chest and/or more frequent and deeper respirations.
  - If exposure continues at that level for several hours, minimal "acidosis" (an acid condition of the blood) may occur but more frequently is absent.
  - The concentration of carbon dioxide usually must be over about 2% (20,000 ppm) before most people are aware of its presence unless the odor of an associated material (auto exhaust or fermenting yeast, for instance) is present at lower concentrations.
- **Breathing rate** doubles at **3%** (**22.8 mmHg**, 30,000 ppm) CO_2 and is four times the normal rate at **5%** (**38 mmHg**, 50,000 ppm) CO_2. **At levels above 5%, concentration CO_2 is directly toxic.** [At lower levels we may be seeing effects of a reduction in the relative amount of oxygen rather than direct toxicity of CO_2.]

Terrestrial Effects

- Symptoms of high or prolonged exposure to carbon dioxide include -rapid breathing, diminished mental alertness, impaired muscular coordination, faulty judgment, depression of all sensations, emotional instability, and fatigue.
- As intoxication progresses, nausea, vomiting, prostration, and loss of consciousness may result.
- Eventually this leads to convulsions, coma, and death.

Main symptoms of

Carbon dioxide toxicity



Research Terrestrially - Navy Data

- Animal Models
  - Animal model- 1.5% (**11.19 mmHg**) CO_2 increased incidence of focal and tubular kidney calcification
  - Animal model 2 –at 1.5% (**11.19 mmHg**) showed significant bone loss of calcium and phosphorus with the commensurate increase in bone bicarbonate to compensate for acidosis.
- Human Data
  - Subject Exposure to 1.5% (**11.19 mmHg**) CO_2 – 42 days increased red cell calcium and renal excretion of Phosphorus. Calcium effect on cell membrane similar to narcosis

  - Schaefer

Research Terrestrially – Navy Data

- Submarine Patrol Data
  - Ten year comparison with Surface Vessels – Increase rate Respiratory, GI, Urologic, and EENT illnesses. $CO_2 \geq 1\%$ (7.6 mmHg) Tansey and Schaefer
  - Royal Navy – Patrols with $CO_2 \geq 1\%$ (7.6 mmHg) showed mild uncompensated respiratory acidosis with the respiratory parameters returning to normal. Pingre

Terrestrial Research

- Animal Models
  - Chronic exposure showed elevated CBF in sheep even after termination of the hypercapnia.
- Human
  - Visuomotor decreases in performance with concentrations of as small as 1.2% (**9.12 mmHg**)

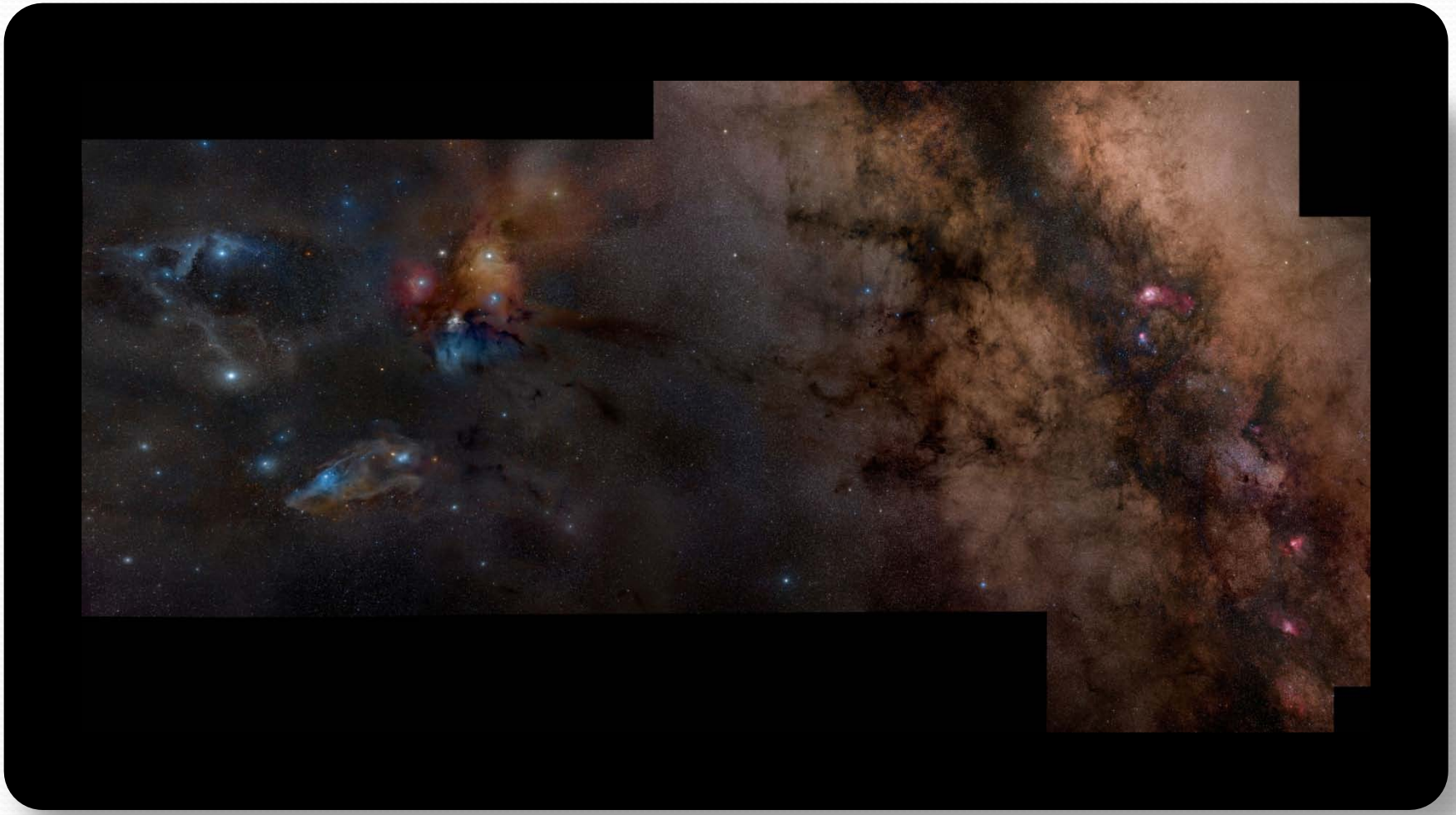
Terrestrial Research

- Chronic Exposure model - 0.7% (**5.32 mmHg**) and 1.2% (**9.12 mmHg**)
  - Showed increased cerebral blood flow, lactic acid build up with exercise, and mild performance impairment
  - Initial response is increased ventilation volume, alveolar dead space, and respiratory rate. Respiratory rate and minute volume return to normal in 2 weeks, but PaCO_2 and pH do not.
  - The CBF decreased after the initial exposure to a higher stabilized baseline. It was also noted that during the CO_2 exposure visual stimulation increased the CBF 30%.
  - Headaches were more frequent at the beginning of the 1.2% CO_2 trial.

Terrestrial Research

- Chronic Exposure model - 0.7% (**5.32 mmHg**) and 1.2% (**9.12 mmHg**)
  - Cerebral autoregulatory mechanisms were preserved during sustained mild and intense exposure levels of hypercapnia (Tested reaction to 5% [38.0 mmHg] during the chronic adaptation phases).
  - The superimposition of Head Down Tilt (HDT) with its increased CBF did not alter CBF responses.
  - Cerebral blood flow responses were similar in amplitude and pattern at both 0.7% (**5.32 mmHg**) and 1.2% (**9.12 mmHg**) CO_2.

Changes in Space



Physiological Changes with Microgravity

- Fluid shift to thorax and head – This results in intracranial pressure increases and congested cerebral circulation – increased CBF and Intravenous dilatation
- Plasma volume – decreased 17% in first 24 hours stabilizes to 15.9 %
- Red cell mass – decreased by 10-11%
- Cardiac output – decreased by 17-20%

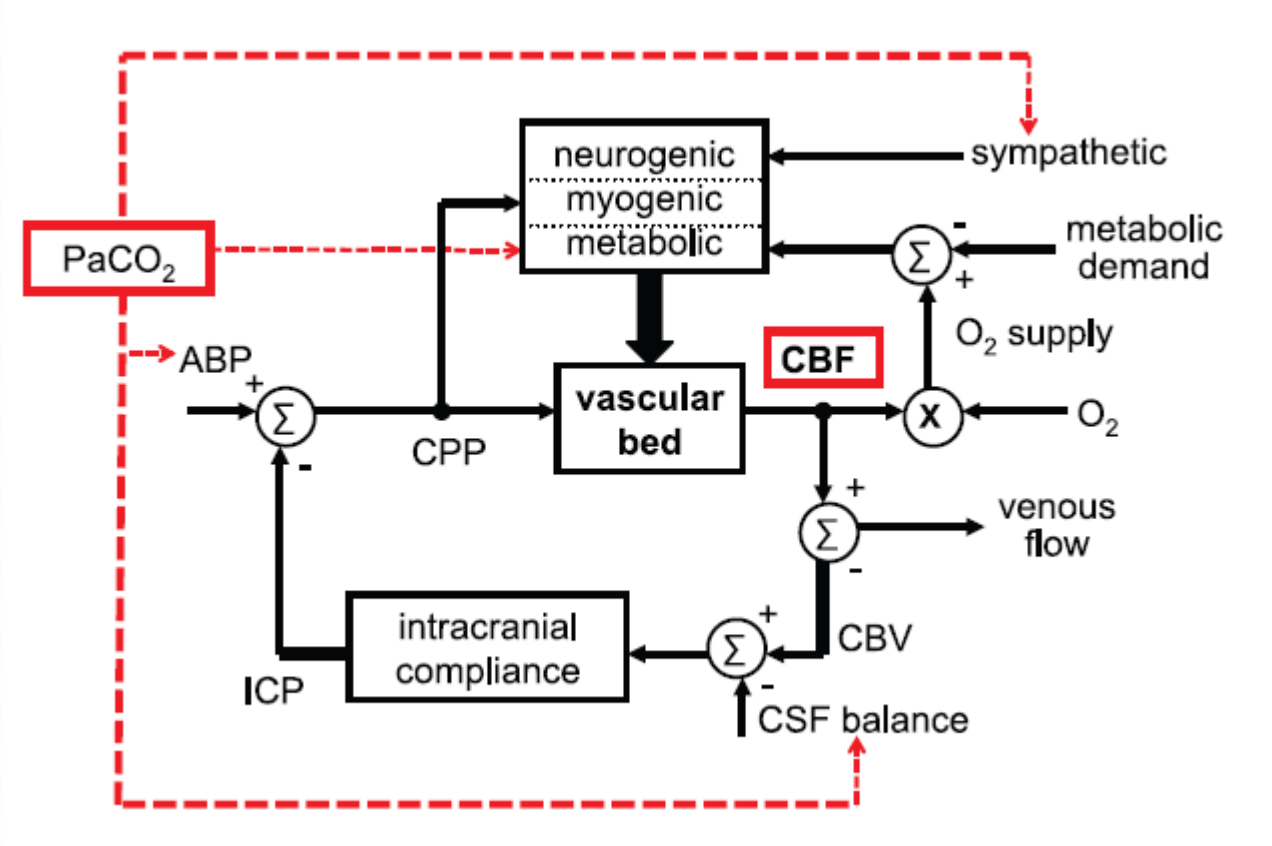
CO_2 Symptoms in space

- Primarily noted to be headache and visual changes.
- Noted onset at levels far lower than terrestrially
- Mission Control personnel noticed behavioral changes had occurred at lower levels in crewmembers. Procedural errors, unwarranted comments from crewmembers, and increased “agrivatioin”
- EVA crewmembers “felt better” post initiation of Oxygen pre-breath and donning the suit (100% O_2 and 4.3 psi environment).

CO_2 Symptoms in space

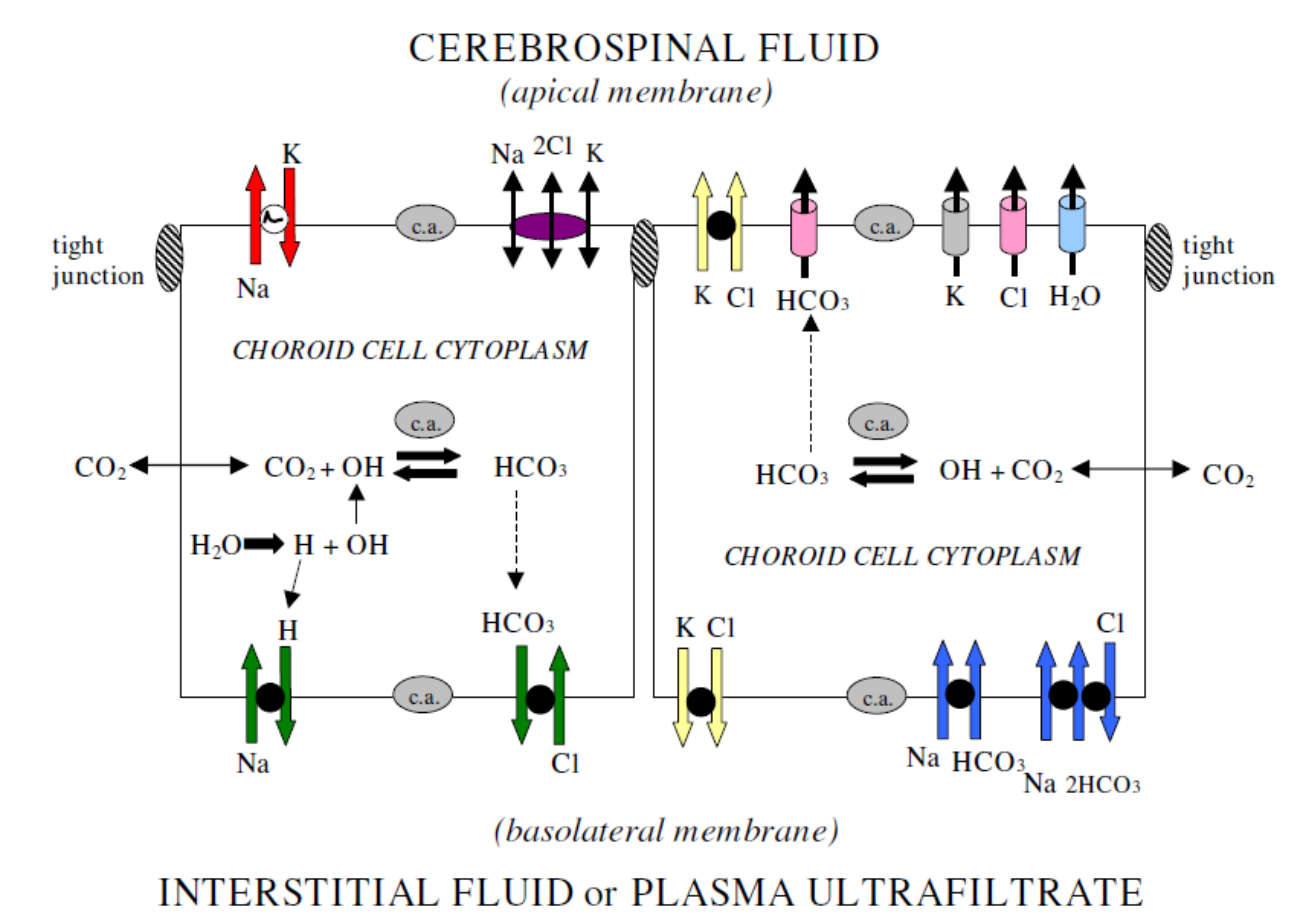
- CO_2 potent vasodilator
- Causes increased blood flow – problem in that the cerebral blood vessels are already congested
- Thought to be contributory to the symptoms occurring at lower levels.

Mechanisms
CO_2 Effects on Cerebral Blood Flow



CSF Production

Blood-CSF Interface in the Choroid Plexus



Neuroendocrine targets of interest

TABLE 1. Receptors Identified in the Choroid Plexus[1]

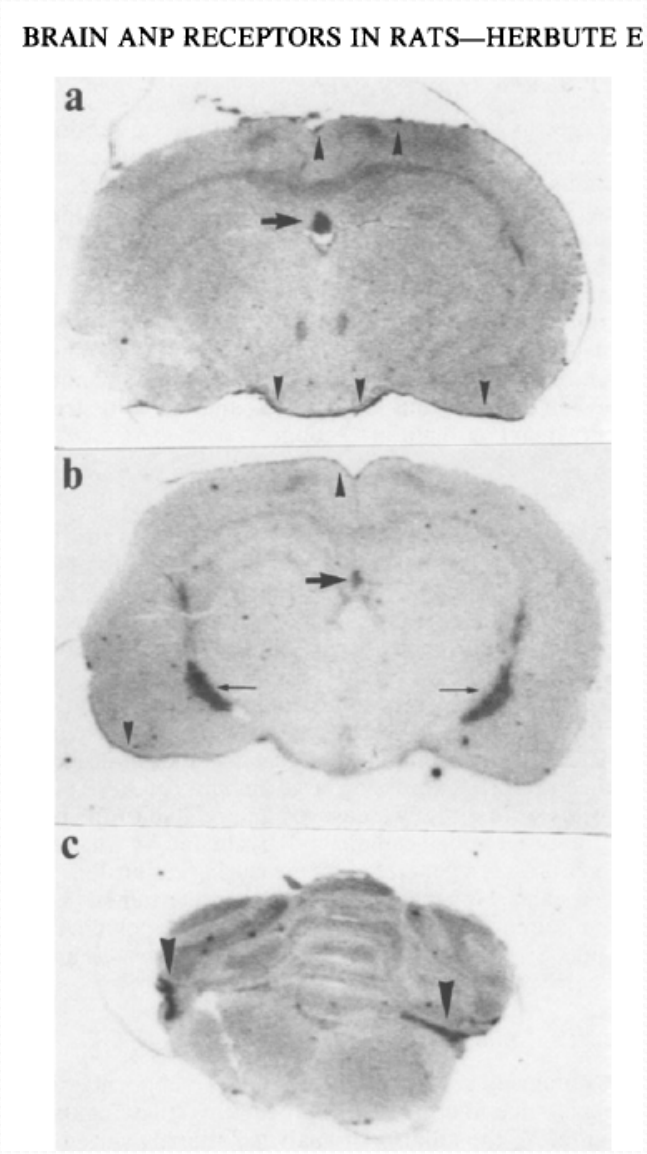
Ligand	Receptor	Method of detection	Selected references
Angiotensin II	AT_{1A}, AT_{1B}	ISH, RGE	Chen et al. (1997) Jöhren and Saavedra (1996)
Apolipoprotein E	apoER2	ISH	Kim, D.-H., et al. (1996)
Apolipoprotein J/clusterin	gp330/megalin	IHC, RT-PCR	Chun et al. (1999) Kounnas et al. (1994)
Atrial natriuretic peptide	NPR-A, NPR-C	AR, ISH	Brown and Zuo (1993) Herman et al. (1996)
Bradykinin	B_2	AR	Murone et al. (1996)
Brain-derived neurotrophic factor	*trk*B, p^{75NTR}	IHC, RPA	Timmusk et al. (1995) Vega et al. (1992)
Corticotropin-releasing factor	CRF-R2	AR, ISH	Chalmers et al. (1995) Lacroix and Rivest (1996) Sanchez et al. (1999)
Endothelin	ET_A, ET_B	ISH, NB, RBA	Angelova et al. (1996, 1997) Hori et al. (1992)
Fibroblast growth factor	FGFR1, FGFR2	ISH	Gonzalez et al. (1995) Yazaki et al. (1994)
Growth hormone	GHR	RBA, RT-PCR	Thörnwall et al. (1995) Zhai et al. (1994)
Insulin	Insulin receptor	AR, ISH	Kar et al. (1993) Marks et al. (1990)
Insulin-like growth factor	IGF-1R, IGF-2R	AR, IHC, RBA	Bondy et al. (1992) Kar et al. (1993) Nilsson et al. (1992)
Interleukin-1	IL-1RI	ISH	Ericsson et al. (1995) Yabuuchi et al. (1994)
Leptin	OB-Rb, OB-Rc, OB-Rf	AR, ISH	Bjorbæk et al. (1998) Corp et al. (1998) Guan et al. (1997)
Nerve growth factor	p^{75NTR}	IHC	Vega et al. (1992)
Neurotrophin-4	*trk*B, p^{75NTR}	IHC, RPA	Timmusk et al. (1995) Vega et al. (1992)
Prolactin	PRL-R	IHC, ISH, RT-PCR	Bakowska and Morrell (1997) Pi and Grattan (1998,1999)
Transforming growth factor-β	TβRII	ISH	Morita et al. (1996) Wang et al. (1995)
Vascular endothelial growth factor	VEGFR-1, VEGFR-2	ISH	Marti and Risau (1998) Millauer et al. (1993) Naito et al. (1995)
Vasoactive intestinal polypeptide	VIP1, VIP2	AR	Vertongen et al. (1997)
Vasopressin	V_{1a}, V_{1b}, V_2[2]	ISH	Burbach et al. (1995) Kato et al. (1995) Ostrowski et al. (1994)

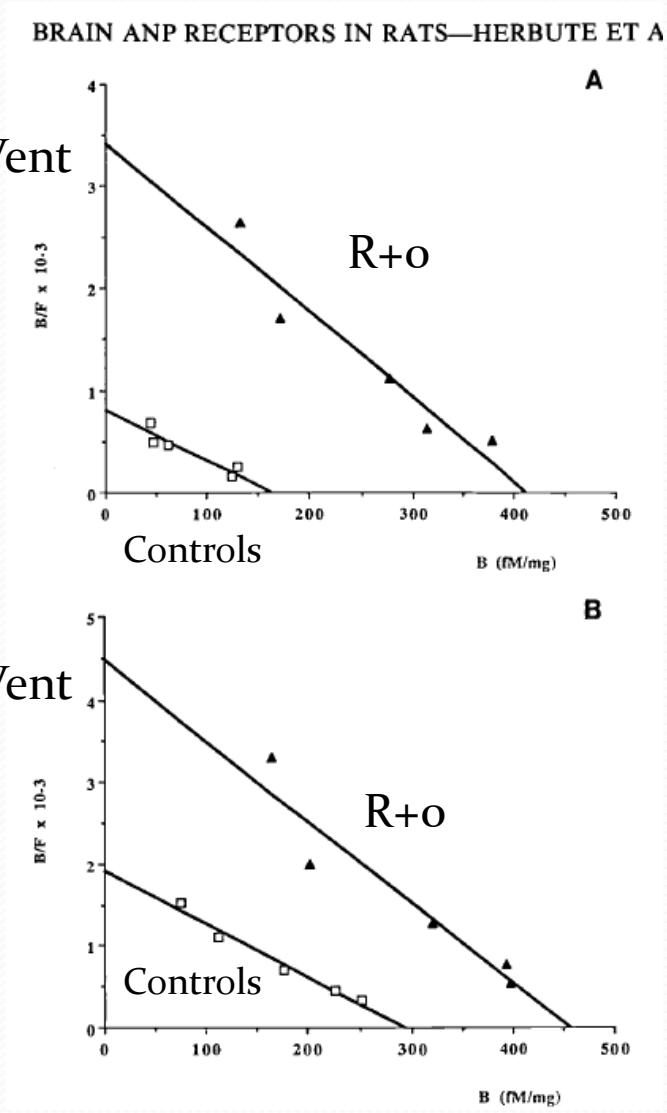
[1]AR = autoradiography; IHC = immunohistochemistry; ISH = in situ hybridization; NB = Northern blotting; RBA = receptor binding assay; RGE = reporter gene expression; RPA = RNase protection assay; RT-PCR = reverse transcriptase-polymerase chain reaction.
[2]Expressed only during development.

What should we be looking for

- Arginine Vasopressin
- Atrial Naturiutetic Peptide

ANP Upregulated in Rat Choroid Plexus After 9 days Spaceflight (STS-40, 1994)



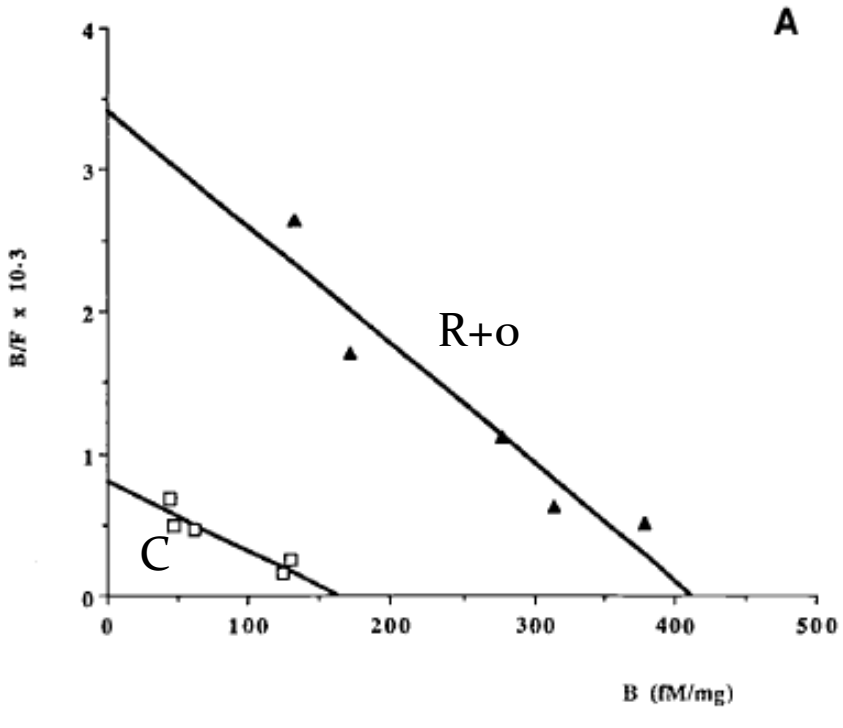


Lat Vent

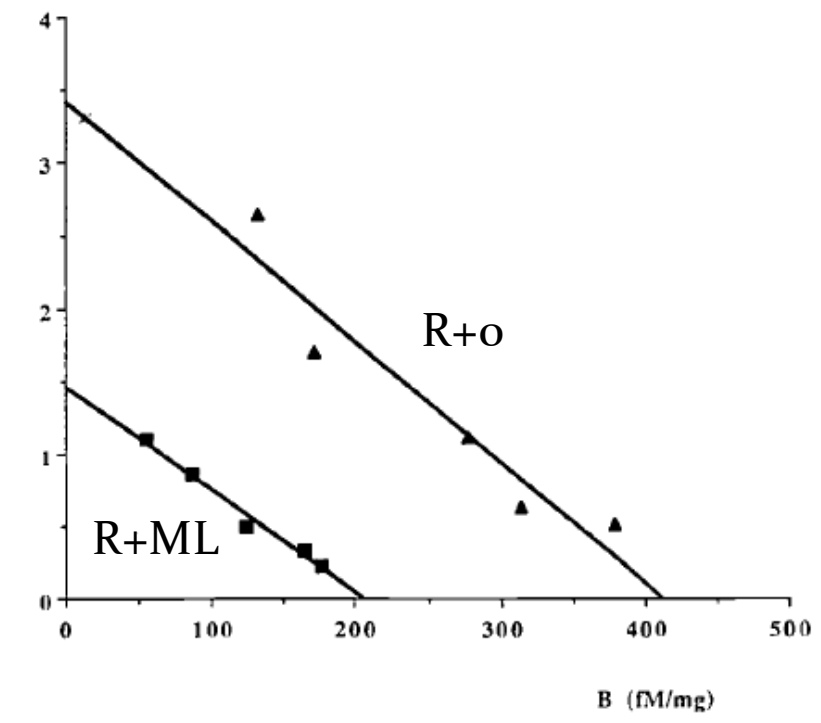
3rd Vent

ANP Expression Returns to Normal Values After Mission Length (ML) Recovery (9 days)

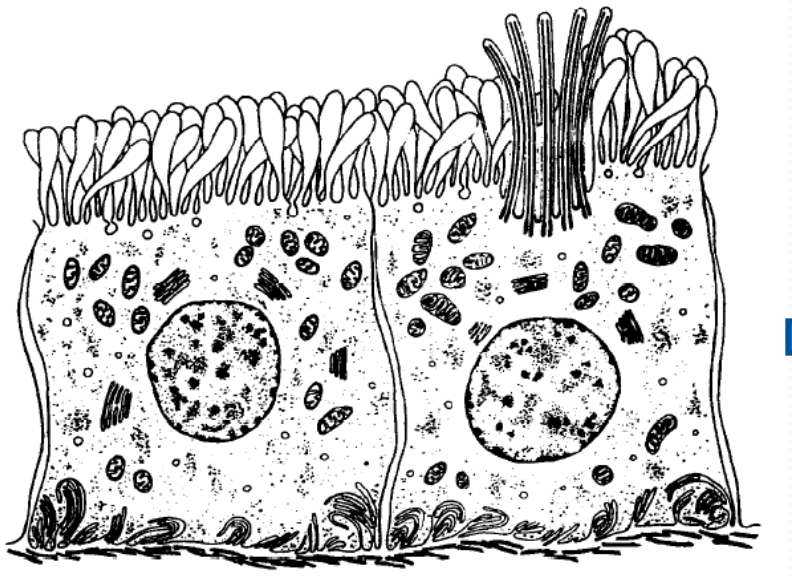
Lat Vent



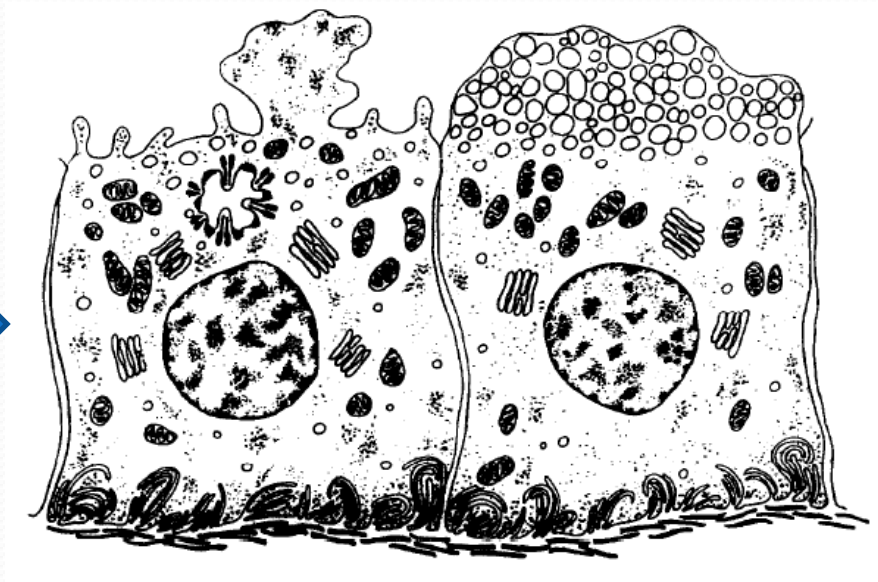
Lat Vent



STS-56 - 1995



Normal



Spaceflight, or Hind-Limb Unloading

Mission-Length Recovery Period