CO$_2$ Effects in Space

Relationship to Intracranial Hypertension
CO₂ Effects Terrestrially

- Terrestrial atmospheric CO₂ 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) CO₂ and is four times the normal rate at 5% (38 mmHg, 50,000 ppm) CO₂. **At levels above 5%, concentration CO₂ 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 CO₂.]
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

**Volume % in air**
- 1%
- 3%
- 5%
- 8%

**Visual**
- Dimmed sight

**Auditory**
- Reduced hearing

**Respiratory**
- Shortness of breath

**Muscular**
- Tremor

**Central**
- Drowsiness
- Mild narcosis
- Dizziness
- Confusion
- Headache
- Unconsciousness

**Skin**
- Sweating

**Heart**
- Increased heart rate and blood pressure
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
Research Terrestrially – Navy Data

- Submarine Patrol Data
  - Ten year comparison with Surface Vessels – Increase rate Respiratory, GI, Urologic, and EENT illnesses. $\text{CO}_2 \geq 1\%$ (7.6 mmHg) Tansey and Schaefer
  - Royal Navy – Patrols with $\text{CO}_2 \geq 1\%$ (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 PaCO₂ and pH do not.
  - The CBF decreased after the initial exposure to a higher stabilized baseline. It was also noted that during the CO₂ exposure visual stimulation increased the CBF 30%.
  - Headaches were more frequent at the beginning of the 1.2% CO₂ 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) CO₂.
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%
CO₂ 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-breathe and donning the suit (100% O₂ and 4.3 psi environment).
CO₂ Symptoms in space

- CO₂ 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

CO₂ 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

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Receptor</th>
<th>Method of detection</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II</td>
<td>AT₁A, AT₁B</td>
<td>ISH, RGE</td>
<td>Chen et al. (1997)</td>
</tr>
<tr>
<td>Apolipoprotein E</td>
<td>apoER2</td>
<td>ISH</td>
<td>Jönsson and Sandgren (1994)</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>B₂</td>
<td>AR</td>
<td>Roumas et al. (1994)</td>
</tr>
<tr>
<td>Brain-derived neurotrophic factor</td>
<td>trkB, p75</td>
<td>IHC, RPA</td>
<td>Brown and Zuo (1993)</td>
</tr>
<tr>
<td>Corticotropin-releasing factor</td>
<td>CRF-R₂</td>
<td>AR</td>
<td>Timmusk et al. (1995)</td>
</tr>
<tr>
<td>Endothelin</td>
<td>FTα, FTβ</td>
<td>ISH, NB, RBA</td>
<td>Varga et al. (1996)</td>
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<tr>
<td>Fibroblast growth factor</td>
<td>FGFRI, FGFRII</td>
<td>ISH</td>
<td>Gonzalez et al. (1996)</td>
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<tr>
<td>Growth hormone</td>
<td>GHR</td>
<td>RBA, RT-PCR</td>
<td>Yozikii et al. (1994)</td>
</tr>
<tr>
<td>Insulin</td>
<td>Insulin receptor</td>
<td>AR, ISH</td>
<td>Toshinouye et al. (1995)</td>
</tr>
<tr>
<td>Insulin-like growth factor</td>
<td>IGF-IR, IGF-IR</td>
<td>AR, HIC, RBA</td>
<td>Zhao et al. (1994)</td>
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<td>Interleukin-1</td>
<td>IL-IR1</td>
<td>ISH</td>
<td>Hori et al. (1993)</td>
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<tr>
<td>Nerve growth factor</td>
<td>Nerve growth factor</td>
<td>IHC, RPA</td>
<td>Lernoix and Riess (1996)</td>
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<tr>
<td>Neurotrophin-4</td>
<td>Nerve growth factor</td>
<td>IHC, RPA</td>
<td>Sano et al. (1996)</td>
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<tr>
<td>Proctolin</td>
<td>PRL-R</td>
<td>IHC, ISH, RT-PCR</td>
<td>Roumas et al. (1994)</td>
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<tr>
<td>Transforming growth factor-β</td>
<td>TβRI1</td>
<td>ISH</td>
<td>Murase et al. (1994)</td>
</tr>
<tr>
<td>Vascular endothelial growth factor</td>
<td>VEGFIR, VEGFIR-2</td>
<td>ISH</td>
<td>Morishita et al. (1994)</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>V₁₆, V₁₇, V₂</td>
<td>AR</td>
<td>Miller et al. (1993)</td>
</tr>
<tr>
<td>Vasotocin intestinal polypeptide</td>
<td>V₁₆, V₁₇, V₂</td>
<td>AR</td>
<td>Kato et al. (1993)</td>
</tr>
</tbody>
</table>

1AR = 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.

*Repressed 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)
ANP Expression Returns to Normal Values After Mission Length (ML) Recovery (9 days)
STS-56 - 1995

Normal

Spaceflight, or Hind-Limb Unloading

Mission-Length Recovery Period