CO: The Silent Killer

Heme Oxygenase Pathway

Hemin \rightarrow \text{HO} \rightarrow \text{CO} \rightarrow \text{sGC} \rightarrow \text{cGMP} \rightarrow \text{BVR} \rightarrow \text{Bilirubin}

- Hemin
- Oxygen (O\textsubscript{2})
- Ferritin
- NADPH
- NADP
- Hemin Biliverdin
- Fe\textsuperscript{2+}
- Fe\textsuperscript{3+}
- Biliverdin
- Bilirubin
- sGC
- cGMP
- BVR
How to specifically increase CO without altering HO levels?

- **CORM-1**: Lipid soluble. CO release stimulated by light. "Fast" CO releaser.
- **CORM-2**: Lipid soluble. CO release stimulated by ligand substitution. "Fast" CO releaser.

THE UNIVERSITY OF MISSISSIPPI MEDICAL CENTER
<table>
<thead>
<tr>
<th>CORM-A1 Concentration</th>
<th>Blood COHb (Percentage of baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time Post Administration (min)</td>
</tr>
<tr>
<td></td>
<td>15</td>
</tr>
<tr>
<td>7.5mg/kg</td>
<td>147±10*</td>
</tr>
<tr>
<td>5mg/kg</td>
<td>105±11</td>
</tr>
<tr>
<td>3mg/kg</td>
<td>107±3</td>
</tr>
<tr>
<td>1.5mg/kg</td>
<td>105±12</td>
</tr>
<tr>
<td>iCORM-A1 (7.5 mg/kg)</td>
<td>101±10</td>
</tr>
</tbody>
</table>
Prevention Study


* p < 0.05 from HF groups
# p < 0.05 from HF + iCORM-A1
Reversal Study

CORM Treatment Decreases Fat Mass (Reversal Study)

How Does CORM-A1 Promote Weight Loss?

- Food Intake
- Metabolism
- Activity
CORM-A1 Treatment has No Effect on Food Intake

Food Intake (grams/day)

Prevention

Reversal

Weeks of Treatment

CORM-A1 Treatment Increases Oxygen Consumption

**Prevention**

- Control
- High Fat + CORM-A1
- High Fat + iCORM-A1

**Reversal**

- Control, n=4
- Saline, n=8
- iCORM-A1, n=8
- CORM-A1, n=8

CORM-A1 Treatment Increases Oxygen Consumption
CORM-A1 Has No Effect on Motor Activity

CORM-A1 Remodels Visceral Adipocytes

Adipocyte size (μm²)

Adipocyte number (cells/μm²)

* = P<0.05 as compared to HFD
# = P<0.05 as compared to iCORM-A1
CORM-A1 Remodels Visceral Adipocytes

**Prevention**
- ALDH1A1
- PGC1-α
- NRF1
- UCP1
- β-actin

**Reversal**
- Control
- Saline
- iCORM-A1
- CORM-A1

**Graphs**
- ALDH1A1/actin (A.U.)
- PGC1-α/actin (A.U.)
- NRF1/actin (A.U.)
- UCP1/actin (A.U.)

*Control, n=3
Saline, n=3
iCORM-A1, n=3
CORM-A1, n=3*
Obesity and Inflammation

CORM-A1 Attenuates HFD Induced HMGB1

Prevention

<table>
<thead>
<tr>
<th>Condition</th>
<th>HMGB-1</th>
<th>β-actin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>HF + iCORM-A1</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>HF + CORM-A1</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Lean</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>

Reversal

<table>
<thead>
<tr>
<th>Condition</th>
<th>HMGB1/actin (A.U.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>![Image]</td>
</tr>
<tr>
<td>Saline</td>
<td>![Image]</td>
</tr>
<tr>
<td>iCORM-A1</td>
<td>![Image]</td>
</tr>
<tr>
<td>CORM-A1</td>
<td>![Image]</td>
</tr>
</tbody>
</table>

Nonalcoholic Fatty Liver Disease (NAFLD), A Serious Complication of Obesity.

- Effects 75 to 100 million individuals in U.S.
- Occurs in up to 66% of patients over 50 yrs old with diabetes or obesity
- Emerging cause of liver cancers and cirrhosis
- No U.S.-FDA approved treatments

Rinella, JAMA. 2015;313(22):2263-2273
CORM-A1 Attenuates HFD Induced Fatty Liver-Reversal Study

Major Limitation of Anti-Obesity Drugs: Adverse Cardiovascular Side Effects

- Fenfluramine/phentermine (fen-phen)- pulmonary hypertension, heart valve disease
- Beta-3 Agonists- tachycardia, hypertension
- Melanocortin 4 Receptor Agonists- hypertension
Chronic CO Treatment Lowers Body Weight and Blood Pressure in SHR
What if CO was Inhaled instead of injected?
## Effects of CO exposure

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Symptom</th>
<th>Therapeutic Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 ppm (0.0050%)</td>
<td>Slight headache after 8 hrs constant exposure</td>
<td>Lowers blood pressure; protective against AKI.</td>
</tr>
<tr>
<td>200 ppm (0.02%)</td>
<td>Slight headache after 2 hrs constant exposure</td>
<td>Protective against AKI; Ischemia-reperfusion Injury</td>
</tr>
<tr>
<td>800 ppm (0.08%)</td>
<td>Dizziness, nausea, and convulsions within 45 min; unconscious within 2 hours</td>
<td>None</td>
</tr>
<tr>
<td>1,600 ppm (0.16%)</td>
<td>Death in less than 2 hours</td>
<td>None</td>
</tr>
<tr>
<td>3,200 ppm (0.32%)</td>
<td>Death in 30 min</td>
<td>None</td>
</tr>
<tr>
<td>6,400 ppm (0.64%)</td>
<td>Death in &lt;20 min</td>
<td>None</td>
</tr>
<tr>
<td>12,800 ppm (1.28%)</td>
<td>Death &lt; 3 min</td>
<td>None</td>
</tr>
</tbody>
</table>
Inhalation Chamber

Real Time Monitoring of Chamber CO Levels

CO flow regulator

Air Outflow

CO Intake

CO Detector
Time Course of Blood COHb Levels Following CO Inhalation Therapy

![Graph showing the time course of blood COHb levels following CO inhalation therapy. The x-axis represents the time post-inhalation (Min) and the y-axis represents the percentage of HbCO (%). The graph includes bars for Basal, 200 ppm, 1 hr, 50 ppm, 2 hrs, and 20 ppm, 2 hrs conditions at 0, 60, and 90 minutes. There are asterisks indicating statistical significance.]
Effect of CO Inhalation on Body Weight

* = p<0.05 as compared to HFD treated
# = p<0.05 as compared to HFD Control
Effect of CO Inhalation on Body Weight

Time (weeks)

\* = p<0.05 as compared to HFD treated
\# = p<0.05 as compared to HFD Control

Hosick, et. al. BMC Obesity 1-6, 2014.
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