Effects of Diesel Exhaust in a Rat Model of Sleep Apnea

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Pre-existing Cardiovascular Disease and Air Pollution

- Air pollution increases cardiovascular mortality
  - Meuse Valley in Belgium
  - Donora, Pennsylvania
  - The “London Fog” incident of 1952

- Allowable levels of pollution also linked to cardiovascular disease
  - Hospital admissions for heart failure and myocardial infarction strongly correlate with daily PM levels
  - Pre-existing cardiovascular disease increases risk for pollution-induced cardiovascular events.
Impact of Sleep Apnea

- Sleep apnea affects approximately 20% of American adults.
- Sleep apnea appears to cause or exacerbate systemic hypertension.
- Sleep apnea is associated with ischemic heart disease, heart failure, stroke, cardiac arrhythmias, and pulmonary hypertension.

*Sleep apnea might therefore injure blood vessels to make them more susceptible to air pollution-induced damage.*
Rat Model of Sleep Apnea (intermittent hypoxia exposure)

Diagram showing Air, N2, CO2, Intervalometer (90 sec switch), Solenoid, Flow regulator, and a graph showing Oxygen and Carbon Dioxide levels over time.
IH Elicits Hypertension in Rats

Kanagy et al. Hypertension 2001
IH Exposure Increases Plasma ET-1

Kanagy et al Hypertension 2001
ET$_A$-Receptor Blockade Decreases Blood Pressure in IH Rats

![Graph showing the effect of BQ-123 on blood pressure in IH rats](image)

* different from control
IH Mesenteric Arteries Are More Responsive to Endothelin than Sham Arteries

**Graph**: Vasoconstriction (%) vs. [ET-1] M

- **Sham (n=6)**
- **IH (n=7)**

* different from Sham
Sensitivity to PE is not Altered in IH Arteries

\[
\text{Vasoconstriction (\%)} \quad 0 \quad 20 \quad 40 \quad 60 \quad 80 \quad 100 \\
\text{[PE] M} \quad 10^{-8} \quad 10^{-7} \quad 10^{-6} \quad 10^{-5}
\]

- Control (n=6)
- IH (n=6)
Endothelin-Dependent Hypertension IH in Rats

- IH exposure causes endothelin-dependent hypertension in rats.
- IH elevates circulating levels of endothelin.
- IH increases vascular sensitivity to endothelin.

![Diagram showing the relationship between intermittent hypoxia, plasma ET-1, vascular sensitivity to ET-1, and hypertension.]

- Intermittent hypoxia leads to an increase in plasma ET-1 levels.
- Plasma ET-1 increases vascular sensitivity to ET-1.
- Increased vascular sensitivity to ET-1 leads to hypertension.
Exposure to Diesel Exhaust Increases Plasma ET-1

![Bar graph showing plasma ET-1 levels in different conditions]

- Air
- 0.5 mg/m³
- 5.0 mg/m³

Plasma ET-1 (fmol/ml)
Hypothesis

Inhalation of whole DE augments ET-vasoconstriction in ET-sensitized rats.
Mechanism of Endothelin Vasoconstriction

**Arteries and Veins**

ET-1 or ET-3

$\uparrow [\text{Ca}^{2+}] \rightarrow \uparrow \text{NOS activity} \rightarrow \text{NO}$

**Endothelial Cell (Dilation)**

**Arteries & Veins**

ET-1

$\uparrow [\text{Ca}^{2+}] \rightarrow \uparrow \text{Crossbridge Cycling} \rightarrow \text{Contraction}$

**Smooth Muscle Cell (Contraction)**
Proposed Actions of DE in IH-Exposed Rats

- Diesel Exhaust

  - Reactive oxygen species

- IH Treatment

  - ↑ Vascular ET receptors
  - ↓ NO
  - ↑ ET-1/3

  - ↑ Vascular sensitivity to endothelin
  - ↓ Vasodilation
  - ↑ Vaso-Constriction
  - ↑ Vascular Resistance
Diesel Exhaust Increases Oxidative Stress

Plasma [TBARs] (nmol/ml)

- Air
- Low DE
- High DE

* Significant difference
Diesel Exhaust Affects Heart Function

Campen et al., Cardiovasc. Tox., 2003
Proposed Mechanism

Diesel Exhaust

Vascular sensitivity to endothelin

Increased Vascular Resistance

IH Treatment

Reactive oxygen species

Vascular ET receptors

NO

ET-1/3

Vasodilation

Vaso-Constriction

Increased Vascular Resistance
Contributors

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