Carbon Monoxide: Toxicity and Potential Therapeutic Agent

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No conflicts of interest to disclose

Carbon monoxide is a colorless, odorless, and tasteless gas

Carbon Monoxide

Leading cause of poison-related mortality in the United States

20,000 ER visits/year
> 2000 hospitalizations/year
~ 6000 deaths/year

Kao LW, Nañagas KA. (2005). Med Clin N Am 89:1161–1194.
Iqbal S, Clower JH, Hernandez SA, Damon SA, Yip FY. (2012). Am J Public Health. 102:1957-63
Centers for Disease Control and Prevention (CDC). (2008). MMWR Morb Mortal Wkly Rep. 57:896-899.

Exogenous CO

Generated by incomplete combustion of carbonaceous fuels

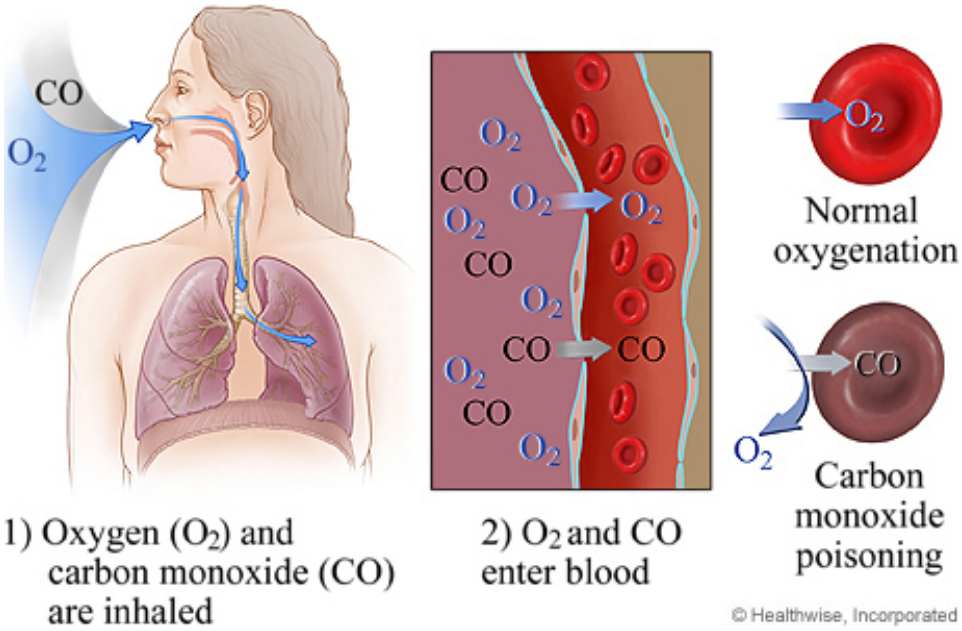
Environmental Sources

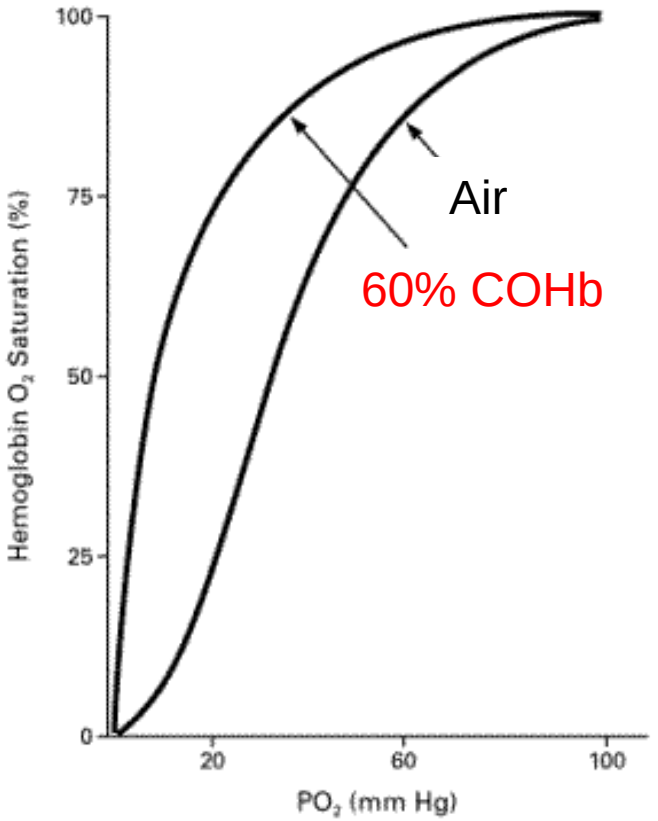
Outdoor sources

- Vehicle exhaust

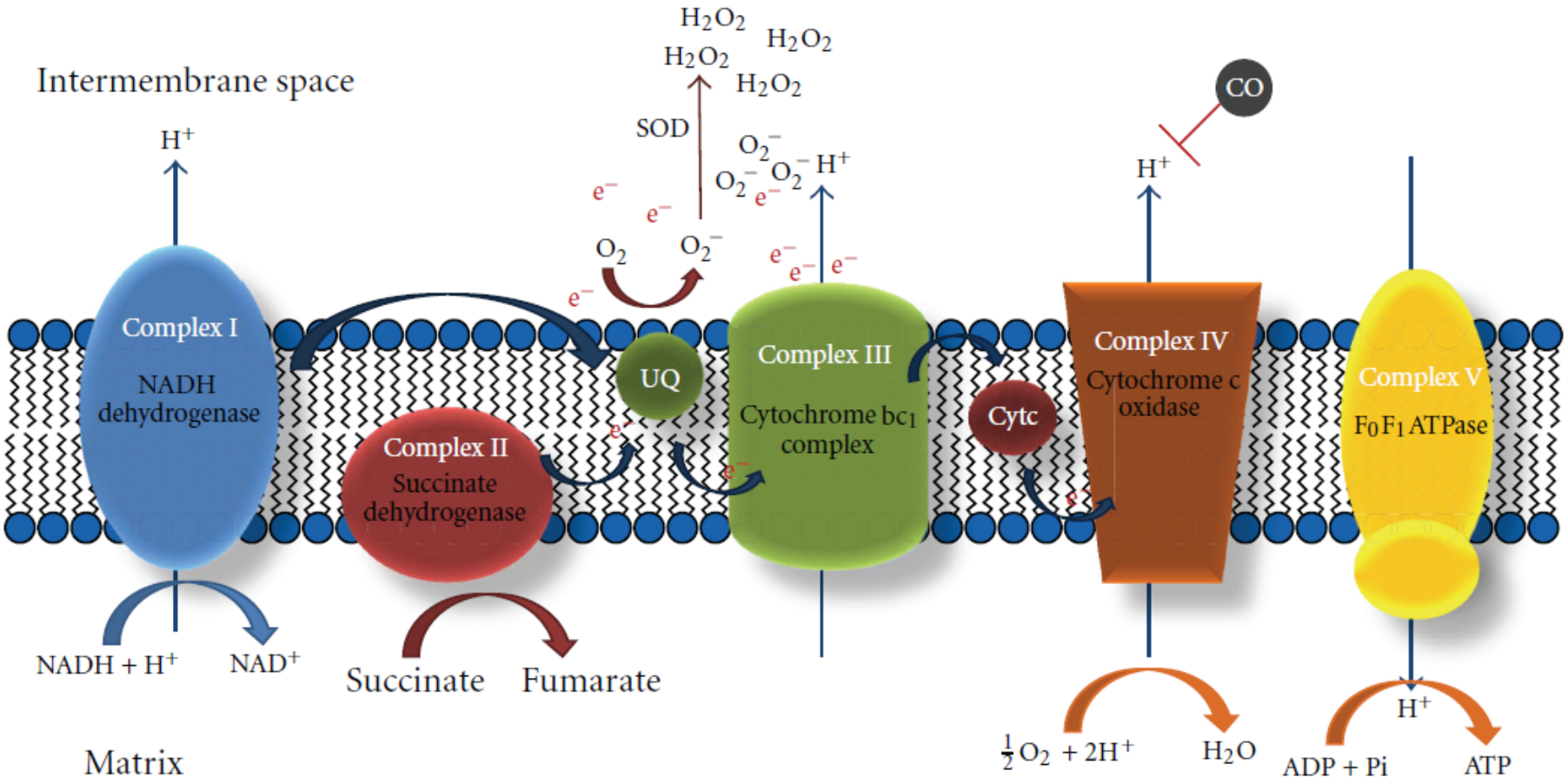
Indoor sources

- Tobacco
- Gas cooking ranges
- Space heaters
- Coal and wood burning stoves
- Generators

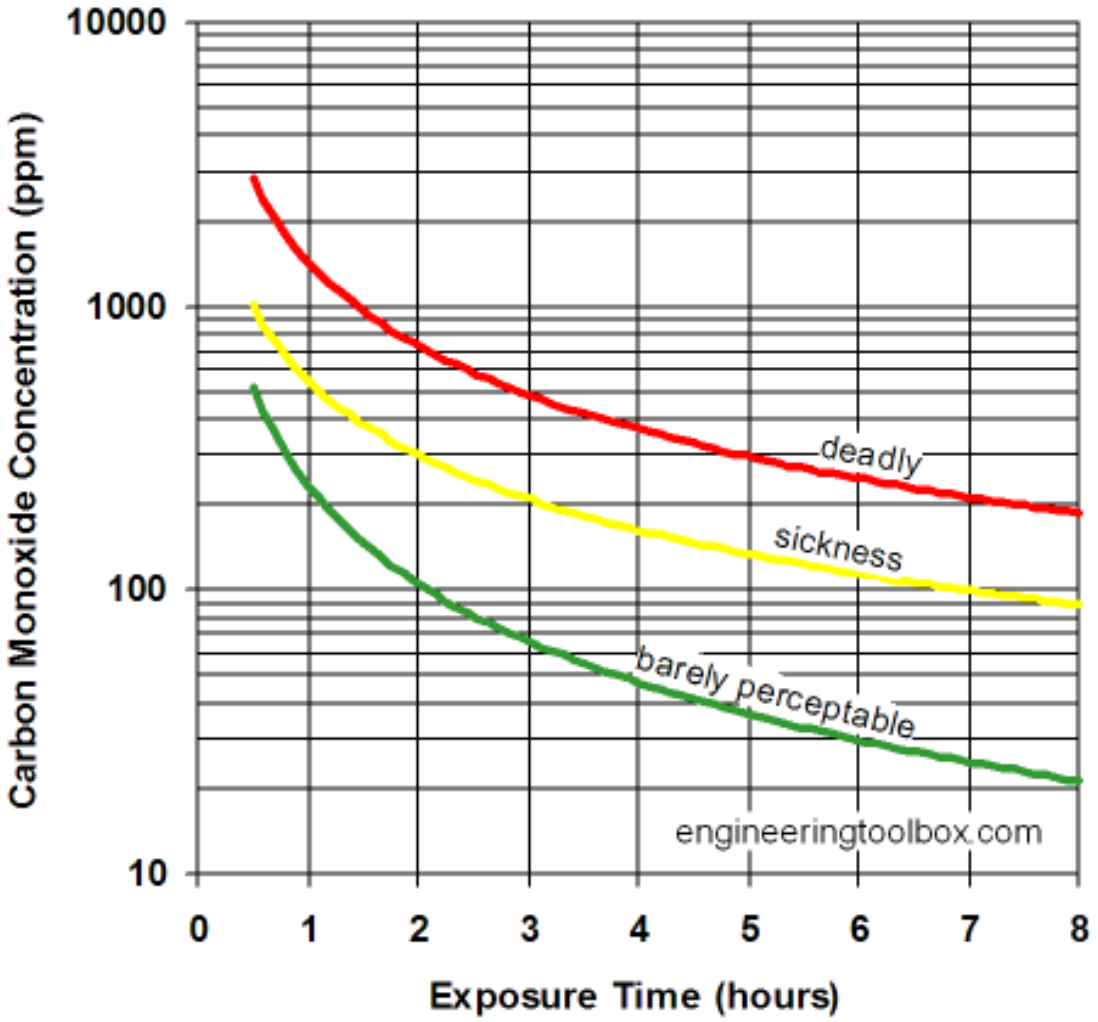




WebMD.com
Ernst A et al. NEJM 1998

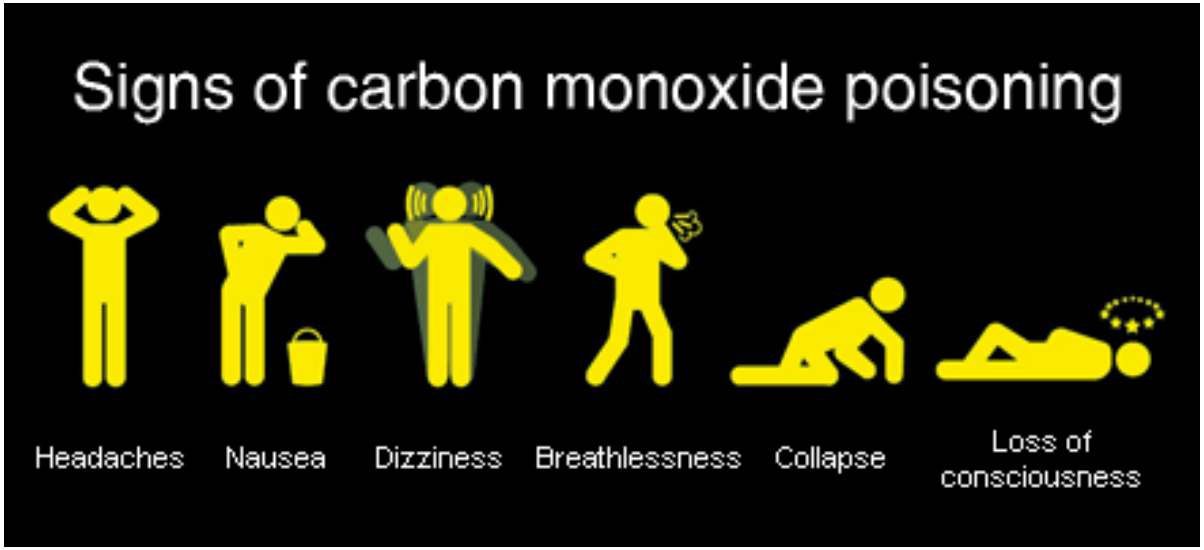


Queiroga CSF et al. Biochemistry Research International. 2012



Coburn-Forster-Kane Model $$\frac{d[COHb]_t}{dt} = \frac{\dot{V}_{CO}}{V_b} + \frac{1}{V_b \beta}\left(P_I CO - \frac{[COHb]_0 P_{\bar{C}} O_2}{[O_2Hb]M}\right)$$

CO in atmosphere (ppm)	COHb in blood (%)	Signs and symptoms
10	2	Asymptomatic
70	10	No appreciable effect, except shortness of breath on vigorous exertion; possible tightness across the forehead; dilation of cutaneous blood vessels.
120	20	Shortness of breath on moderate exertion; occasional headache with throbbing in temples
220	30	Decide headache; irritable; easily fatigued; judgment disturbed; possible dizziness; dimness of vision.
350 - 520	40 – 50	Headache, confusion; collapse; fainting on exertion
800 - 1220	60 – 70	Unconsciousness; intermittent convulsion; respiratory failure, death if exposure is long continued
1950	80	Rapidly fatal



http://www.theaa.com/insurance/carbon-monoxide-gas-safety.html

CO Policy

Outdoor environment - Law

- 1970 US Clean Air Act
- 1971 EPA National Ambient Air Quality Standard
  - 9 ppm CO for 8 hours
  - 35 ppm CO for 1 hour

Indoor environment - Guidelines

- OSHA
  - 50 ppm CO for 8 hours
- NIOSH
  - 35 ppm CO for 8 hours (ceiling of 200 ppm)

US Environmental Protection Agency, 2012

CO production within anesthesia breathing circuits was first reported in 1990

Moon RE, el al; *Anesthesiology*. 1990;73:A109.

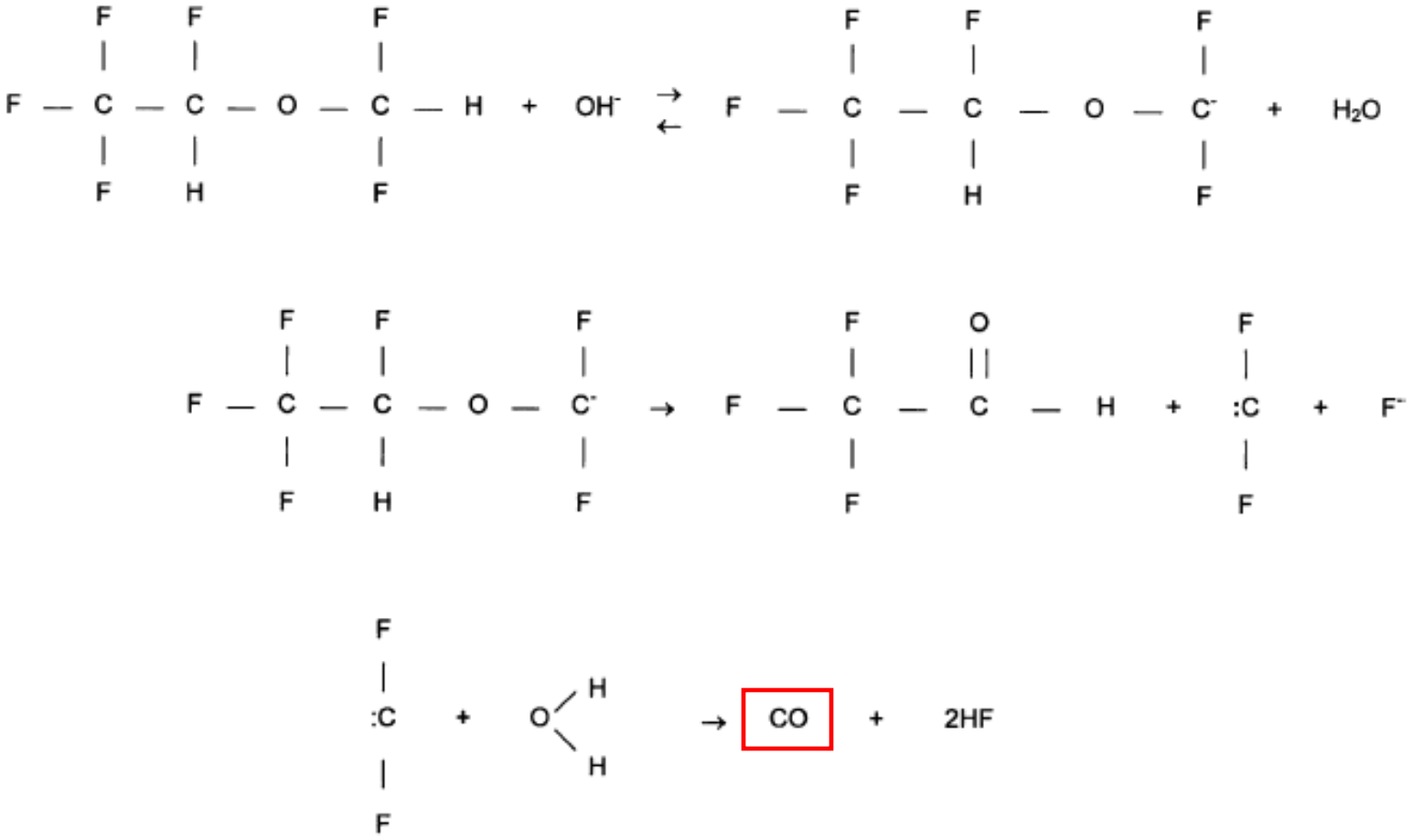


Figure 1 Simplified mechanism of carbon monoxide (CO) formation from desflurane (Baxter); the source of CO is the $-CF_2$ moiety.

Mean peak and median carbon monoxide concentration [CO] in parts per million of the two consecutive experiments for each desiccated carbon dioxide absorbent used in combination with desflurane 3.0 vol%.

CO_2 absorbent	Peak [CO]	Median [CO]
Medisorb®	13,317	2979
Spherasorb®	9045	2273
Loflosorb®	525	318
Superia®	32	20
Amsorb®	0	0
Lithium hydroxide	0	0

Significant differences were found between the 36 median carbon monoxide (CO) concentrations of all absorbents (Kruskall Wallis: $P < 0.001$) except for comparison between Medisorb® – Spherasorb® (Mann–Whitney U test: $P = 0.121$) and Amsorb® – LiOH (Mann–Whitney U test: $P = 1.000$).

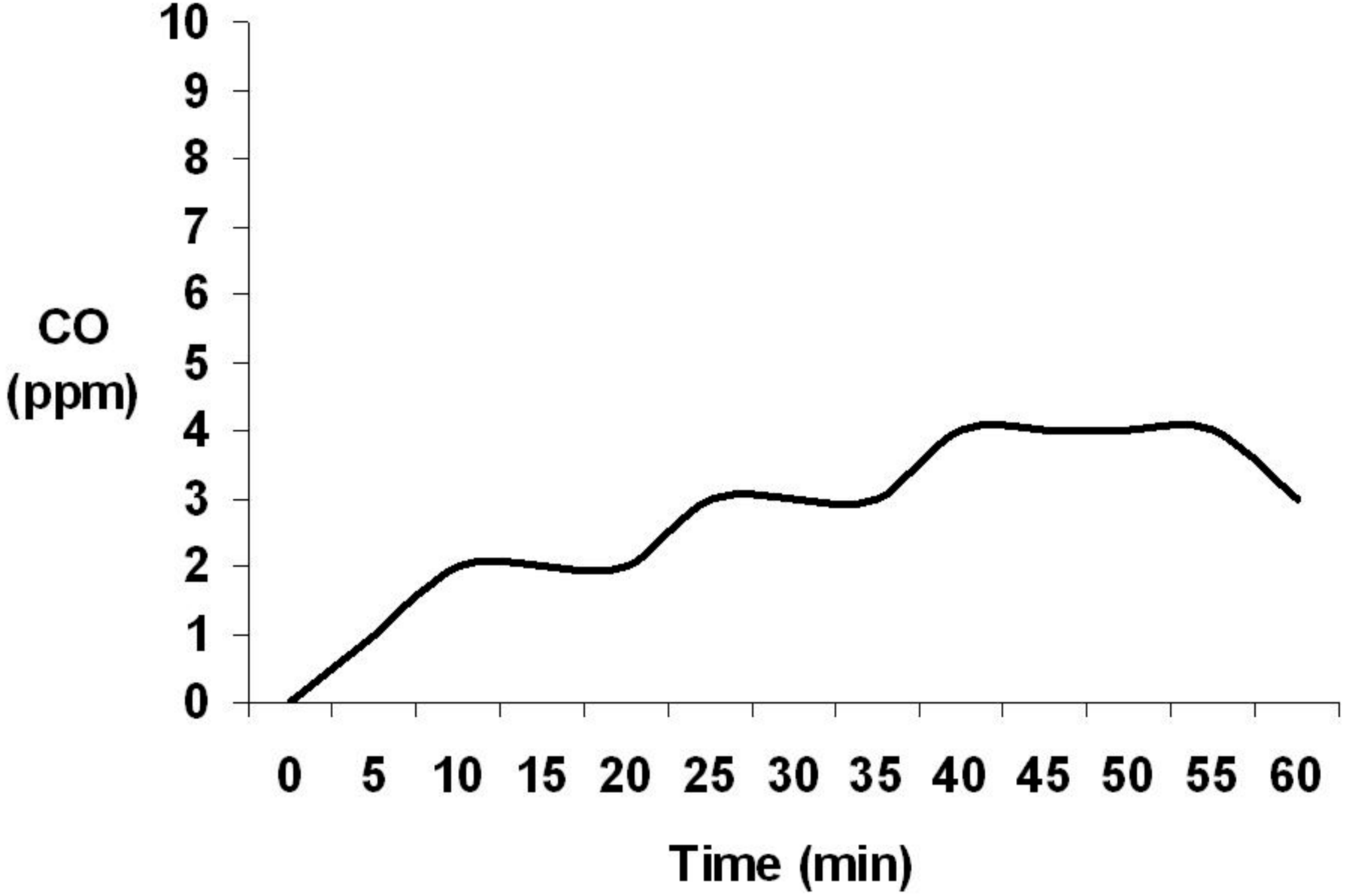
C. KEIJZER, et al. *Acta Anaesthesiol Scand* 2005; 49: 815-818

Table 1. Average Concentrations (ppm/min) of CO Produced by 21–25 g of Soda Lime or Baralyme® Acting on 4% Desflurane, 1.2% Enflurane, or 1.0% Isoflurane Flowing at 12.5 mL/min Through the Absorbent

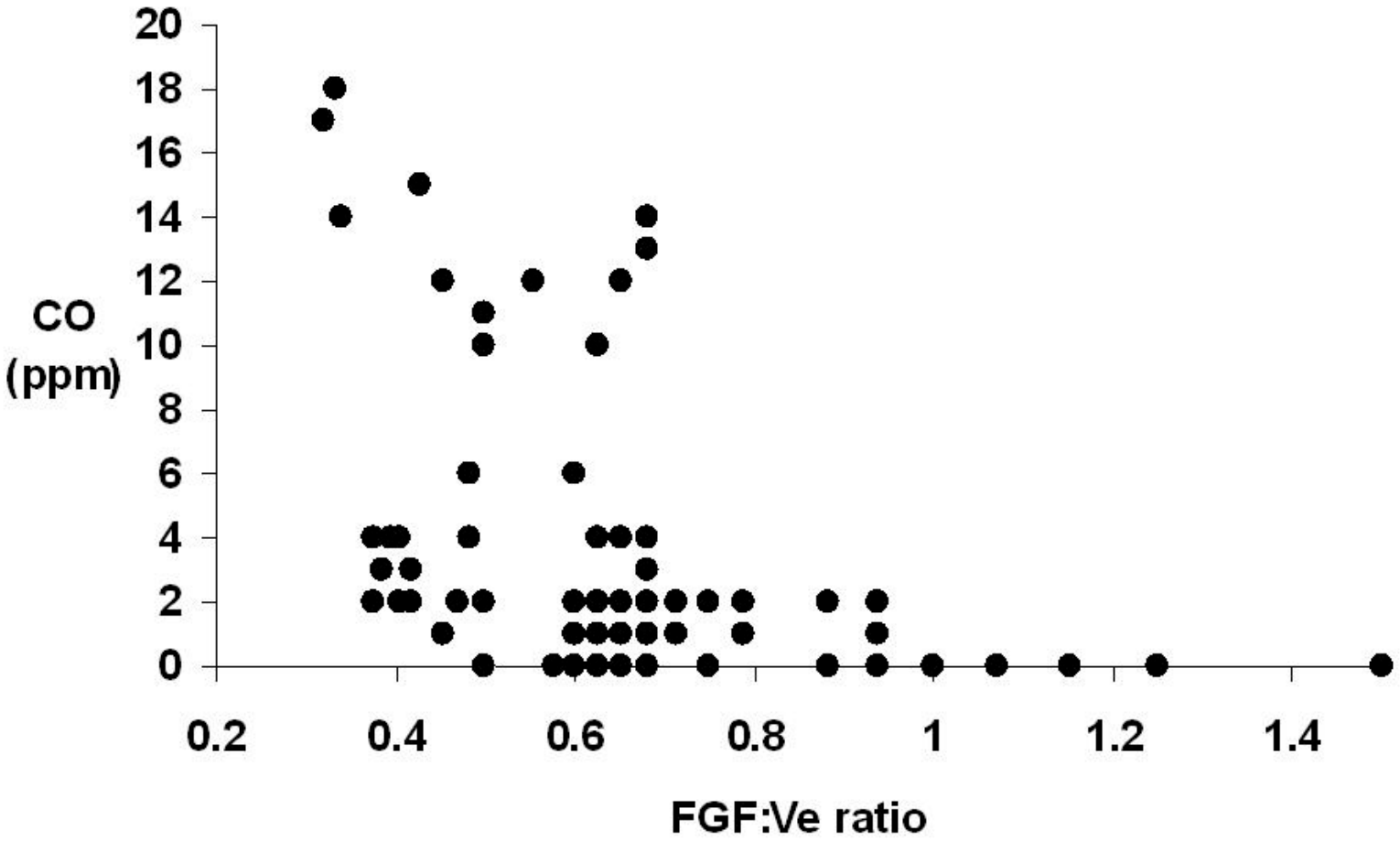
	Duration of anesthetic administration					
	Desflurane		Enflurane		Isoflurane	
Temperature (°C)	2 h	4 h	2 h	4 h	2 h	4 h
Soda lime, dry						
25°C	891	572	1150	744	296	183
35°C	1800	1080	1470	923	349	231
45°C	2490	1470	2200	1320	455	292
Soda lime, 1.4% water						
35°C	26[a]	26[a]	46	57	23	23
45°C	58[a]	80[a]	100	129	104	104
Baralyme®, dry						
25°C	9730	5980	3760	2440	606	549
35°C	11600	7180	4930	3680	851	907
45°C	15200	9310	10100	3780	919	1030
Baralyme®, 1.6% water						
25°C	4100	2760	3170	2200	578	575
35°C	5910	3910	3640	2610	725	766
45°C	7480	4730	4340	3430	871	896
Baralyme®, 3.2% water						
45°C	1410	1220	1430	1100	678	636
Baralyme®, 4.7% water						
45°C	238	247	379	374	237	363

Baralyme® is from Allied Healthcare Products, Inc., St. Louis, MO.
[a] 5% desflurane.

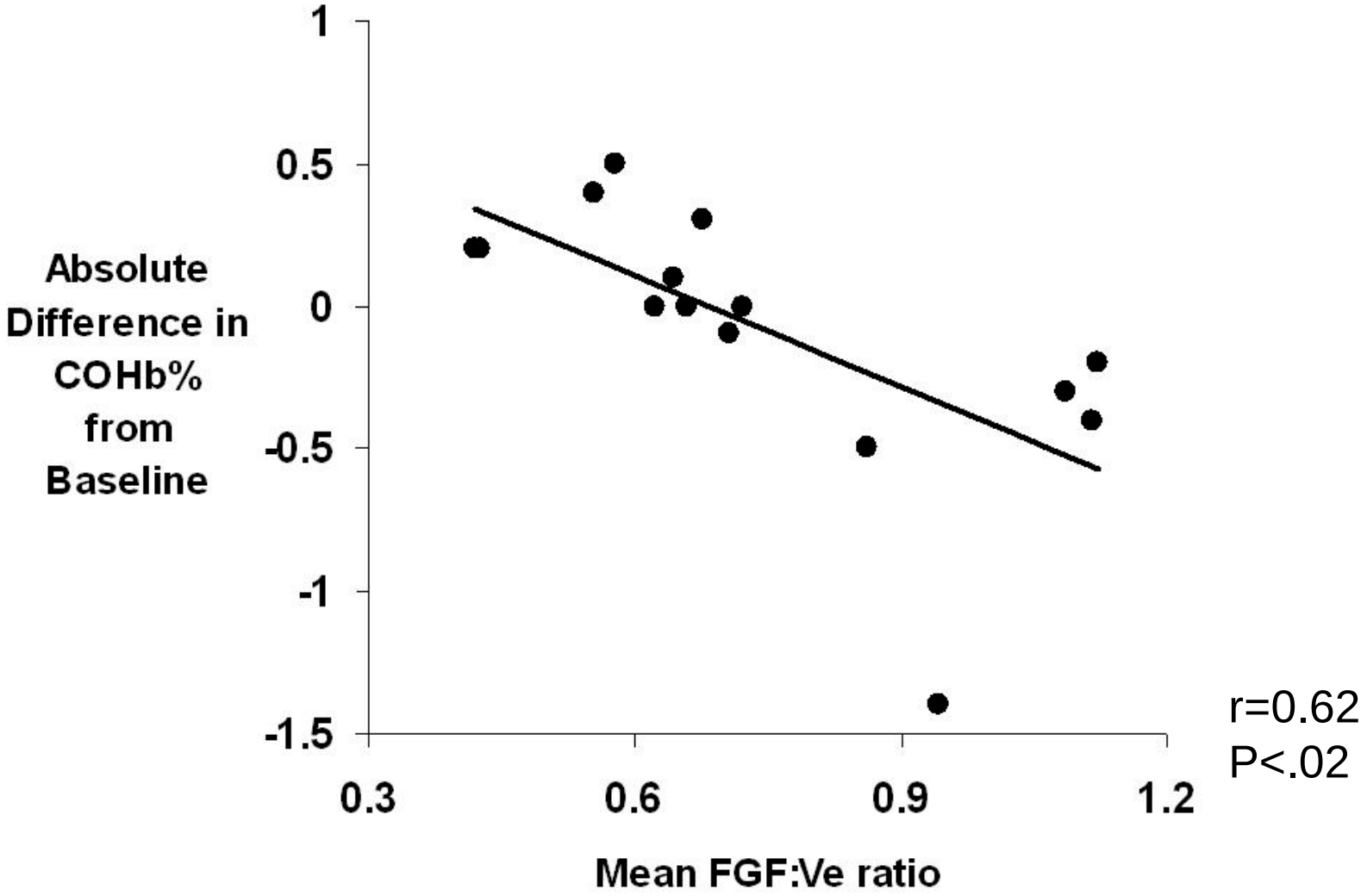
Fang ZX, el al; Anesth Analg 1995;80:1187-93



Levy RJ et al. Anesth Analg. 2010 Mar;110(3):747-53.

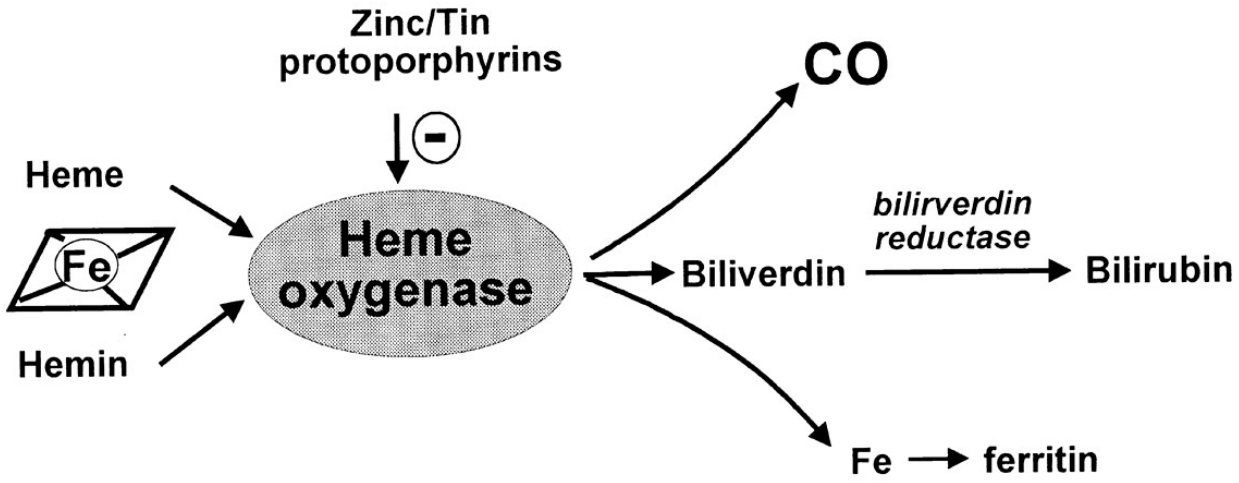


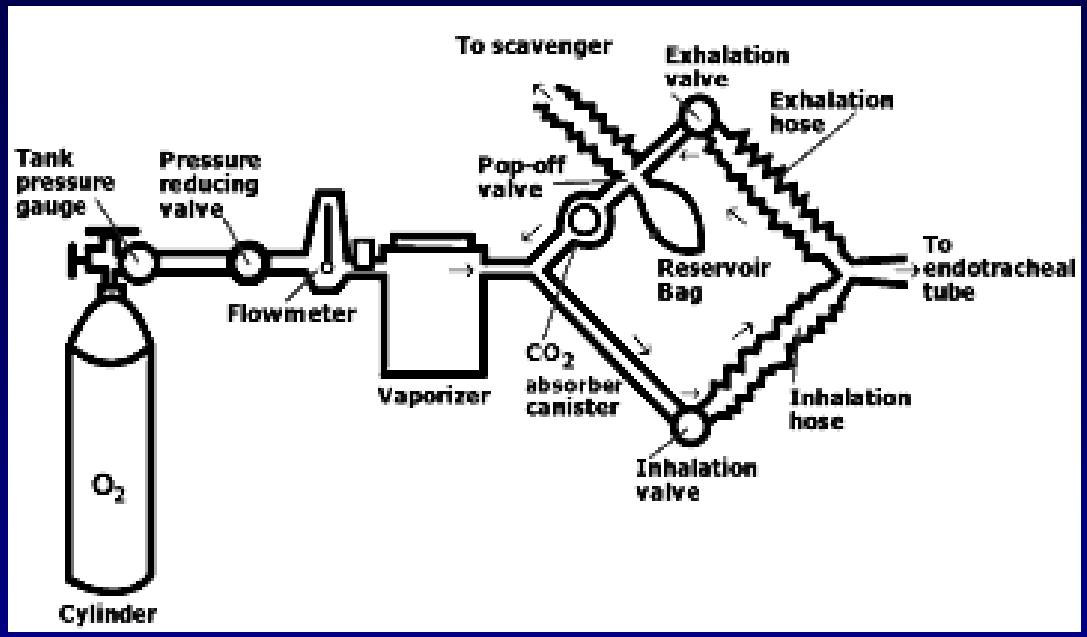
Levy RJ et al. Anesth Analg. 2010 Mar;110(3):747-53.



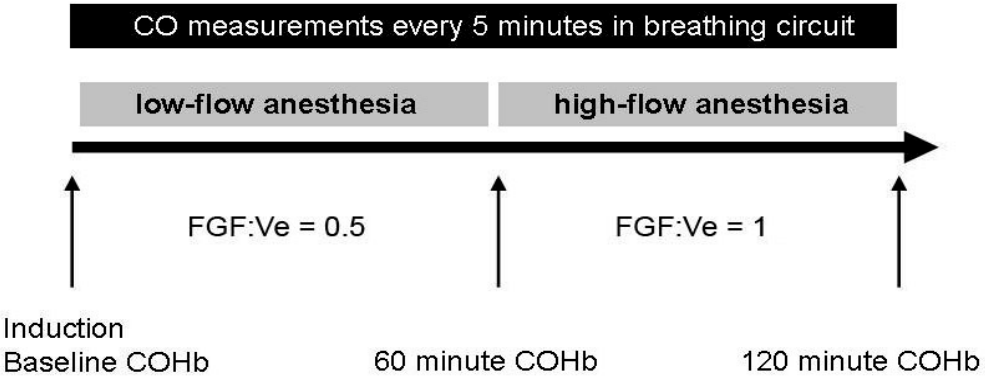
Levy RJ et al. Anesth Analg. 2010 Mar;110(3):747-53.

CO is produced endogenously as well

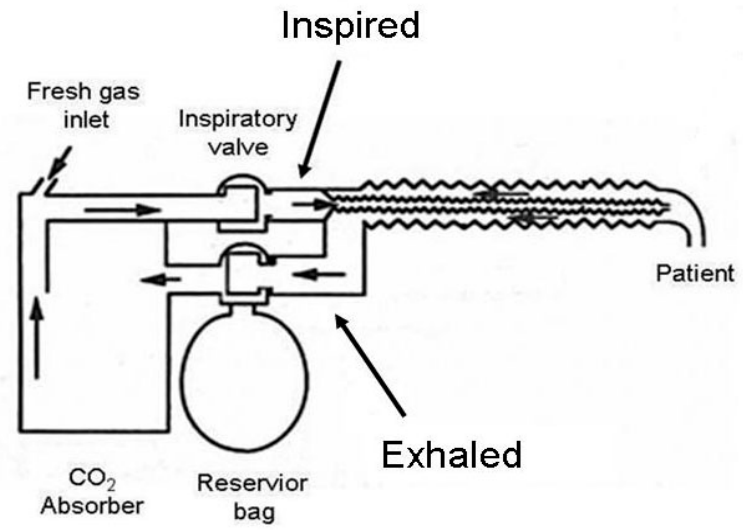



To scavenger
Exhalation valve
Exhalation hose
Tank pressure gauge
Pressure reducing valve
Pop-off valve
To endotracheal tube
Reservoir Bag
Flowmeter
Vaporizer
CO_2 absorber canister
Inhalation hose
Inhalation valve
O_2
Cylinder

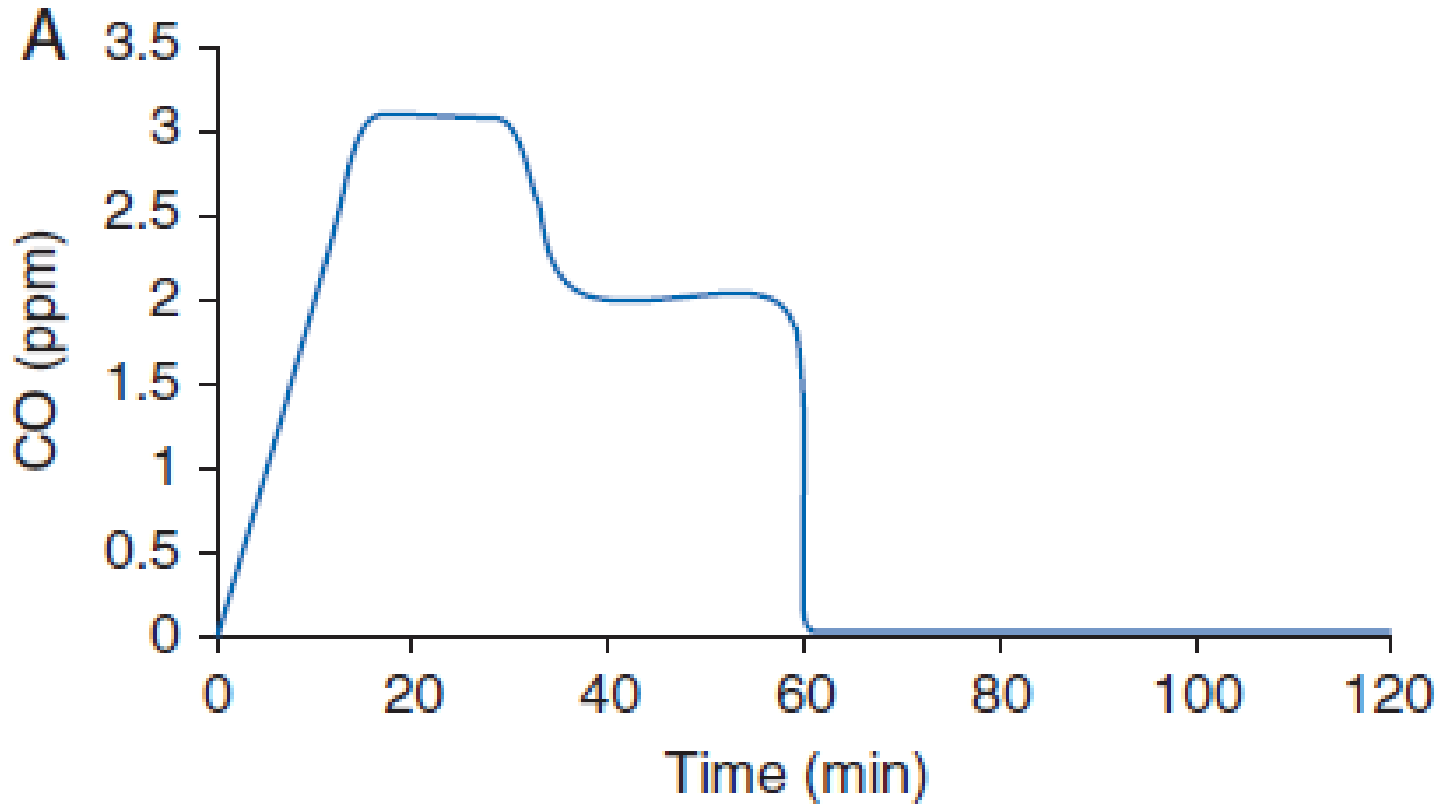
A



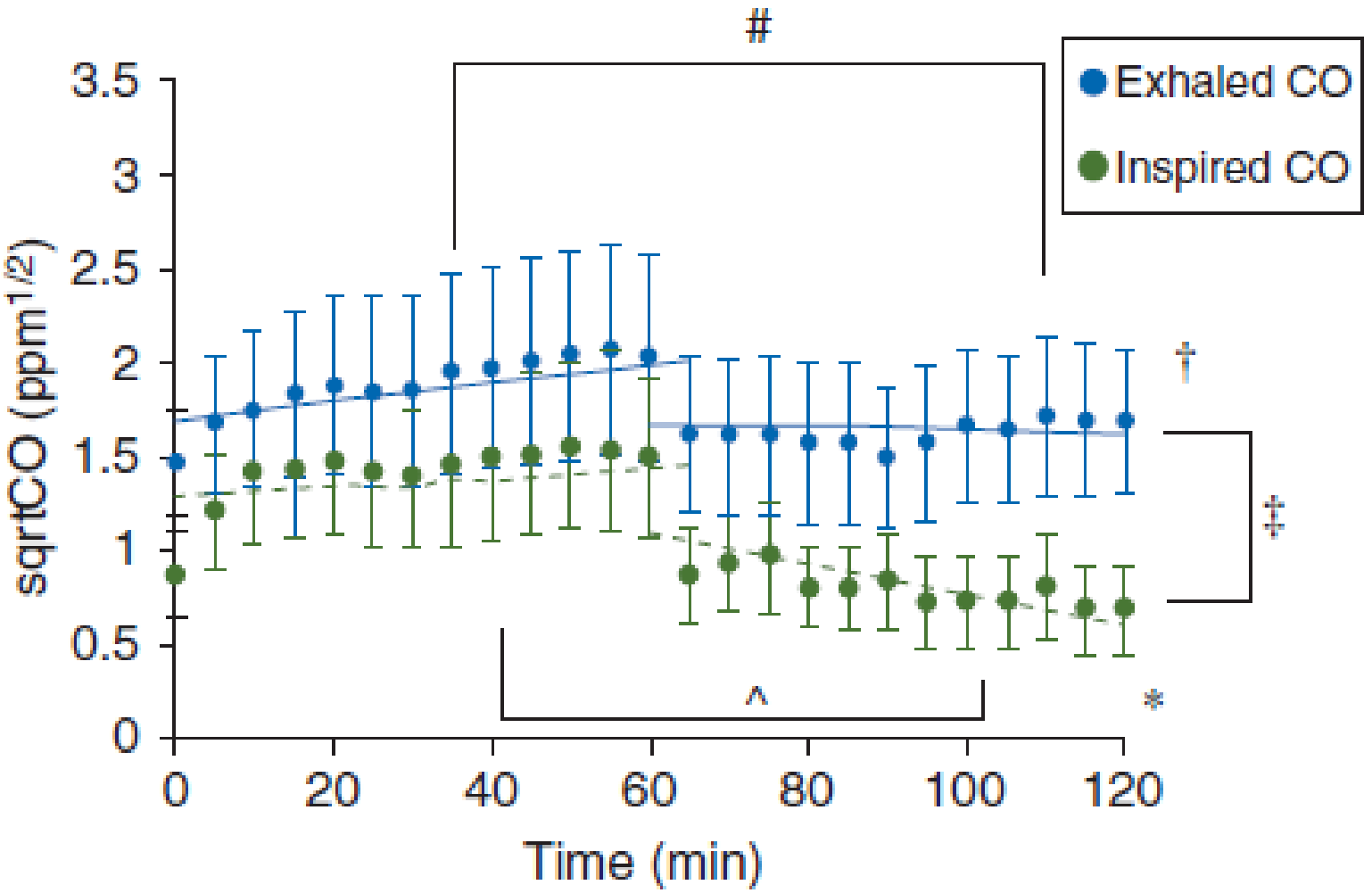
B



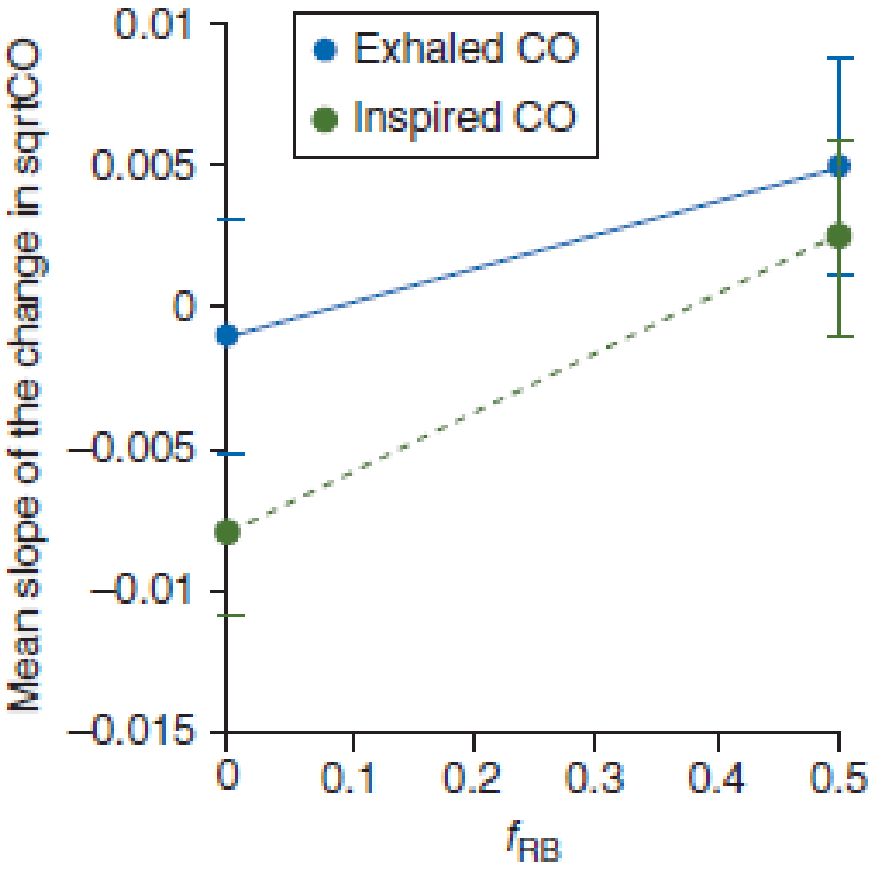
Nasr et al. BJA. 2010 105(6):836-41.



Nasr et al. BJA. 2010 105(6):836-41.

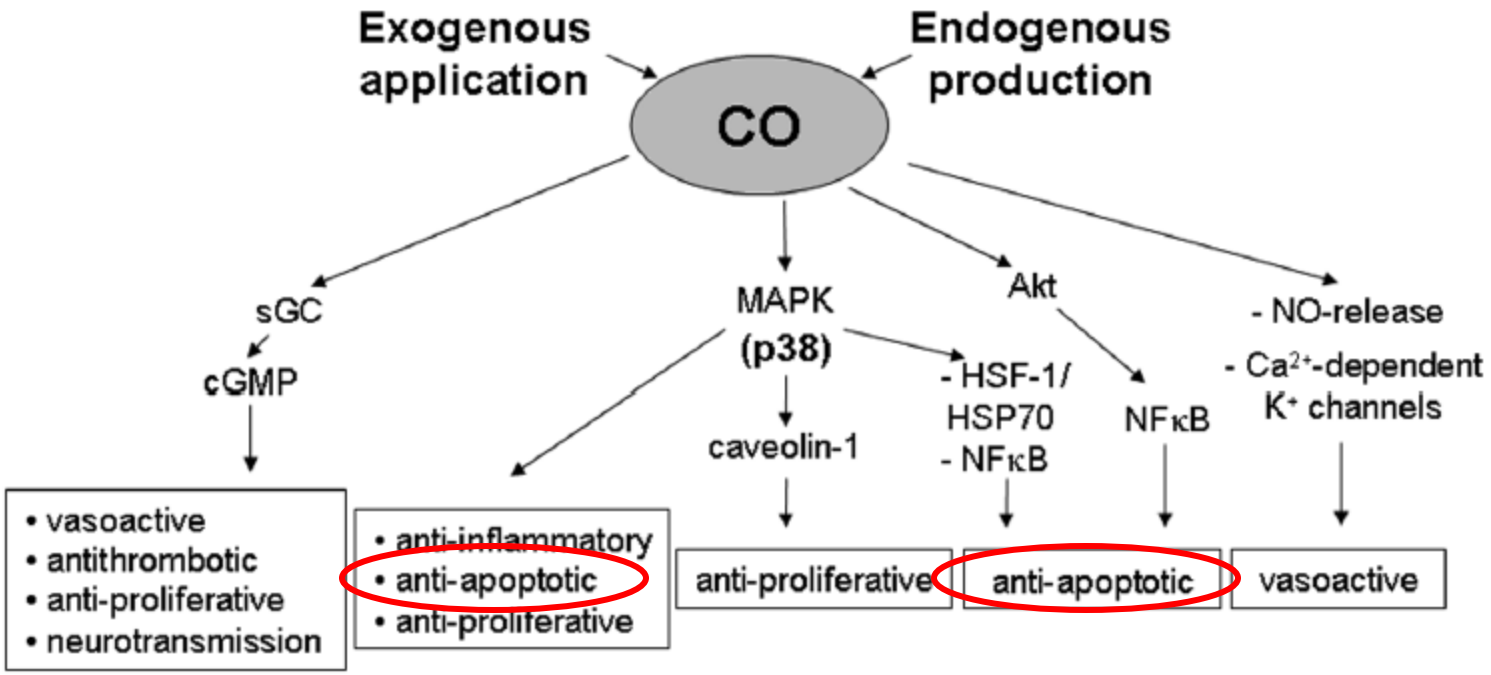


Nasr et al. BJA. 2010 105(6):836-41.

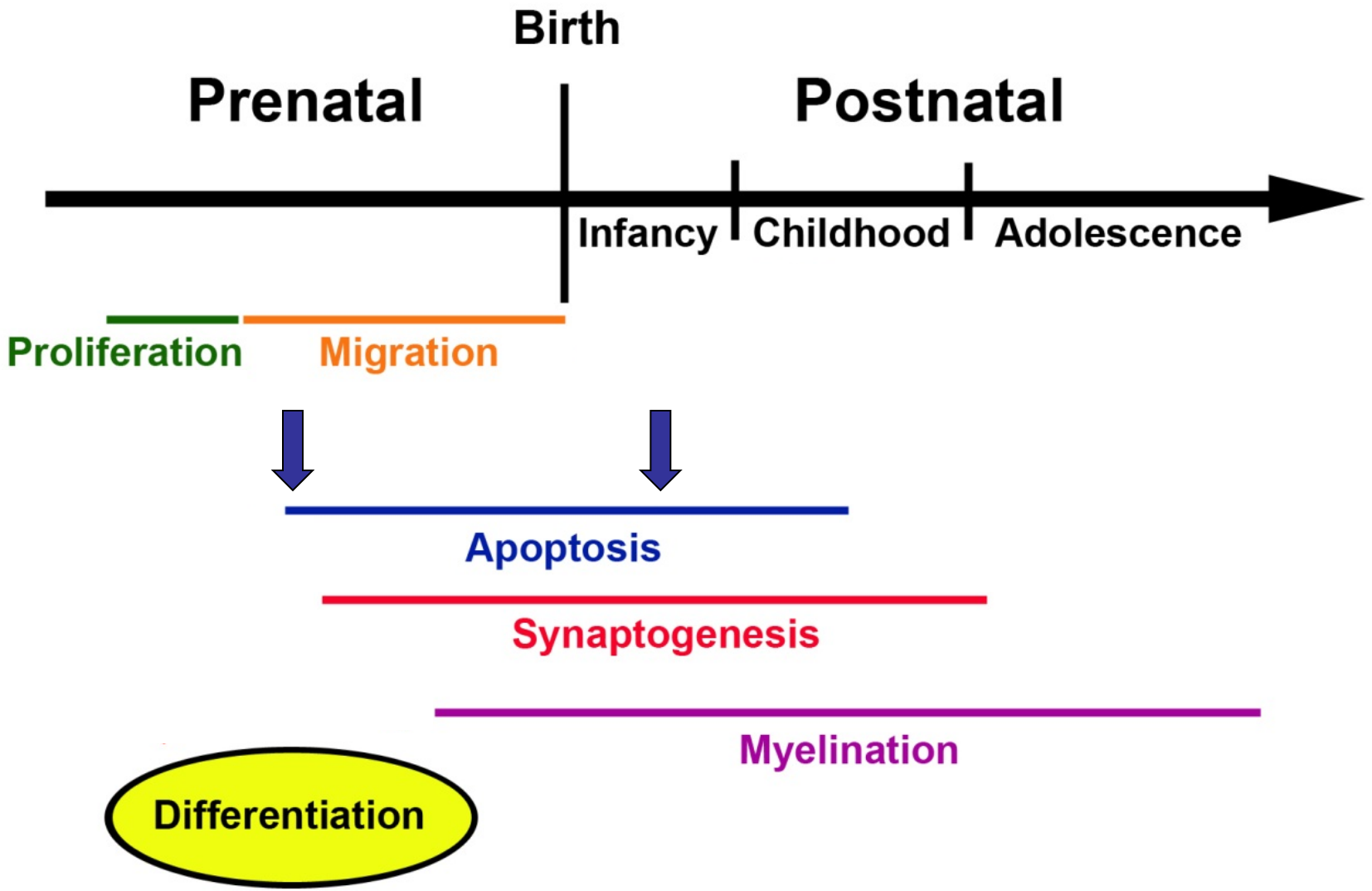


Nasr et al. BJA. 2010 105(6):836-41.

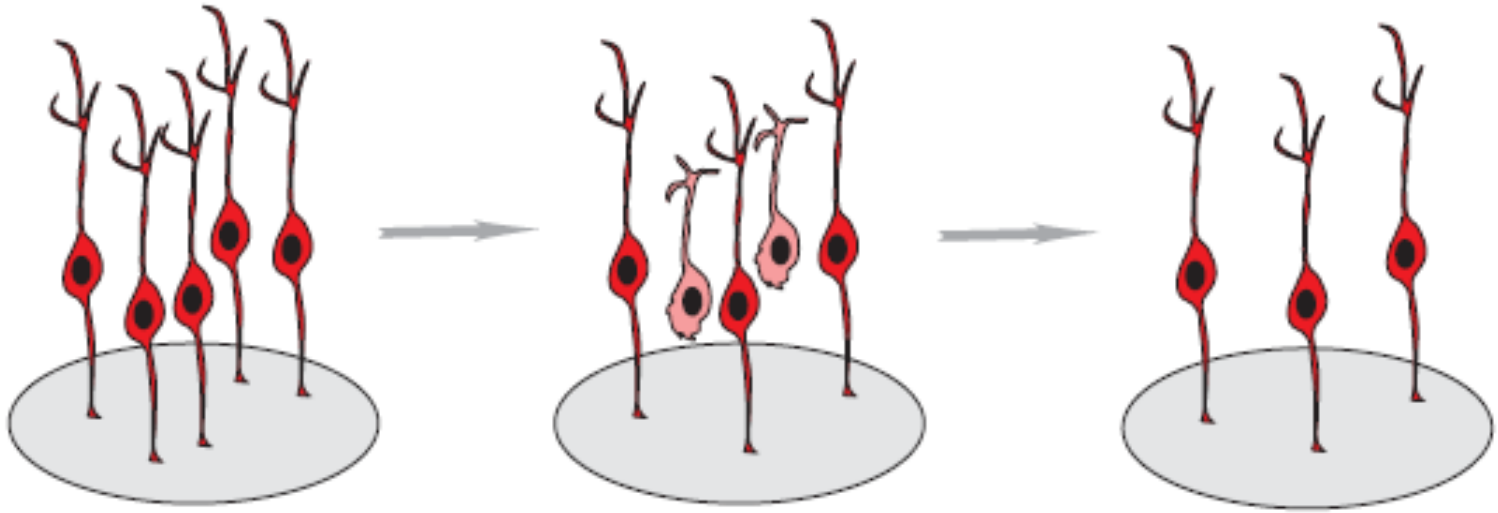
Low dose CO has cellular protective properties



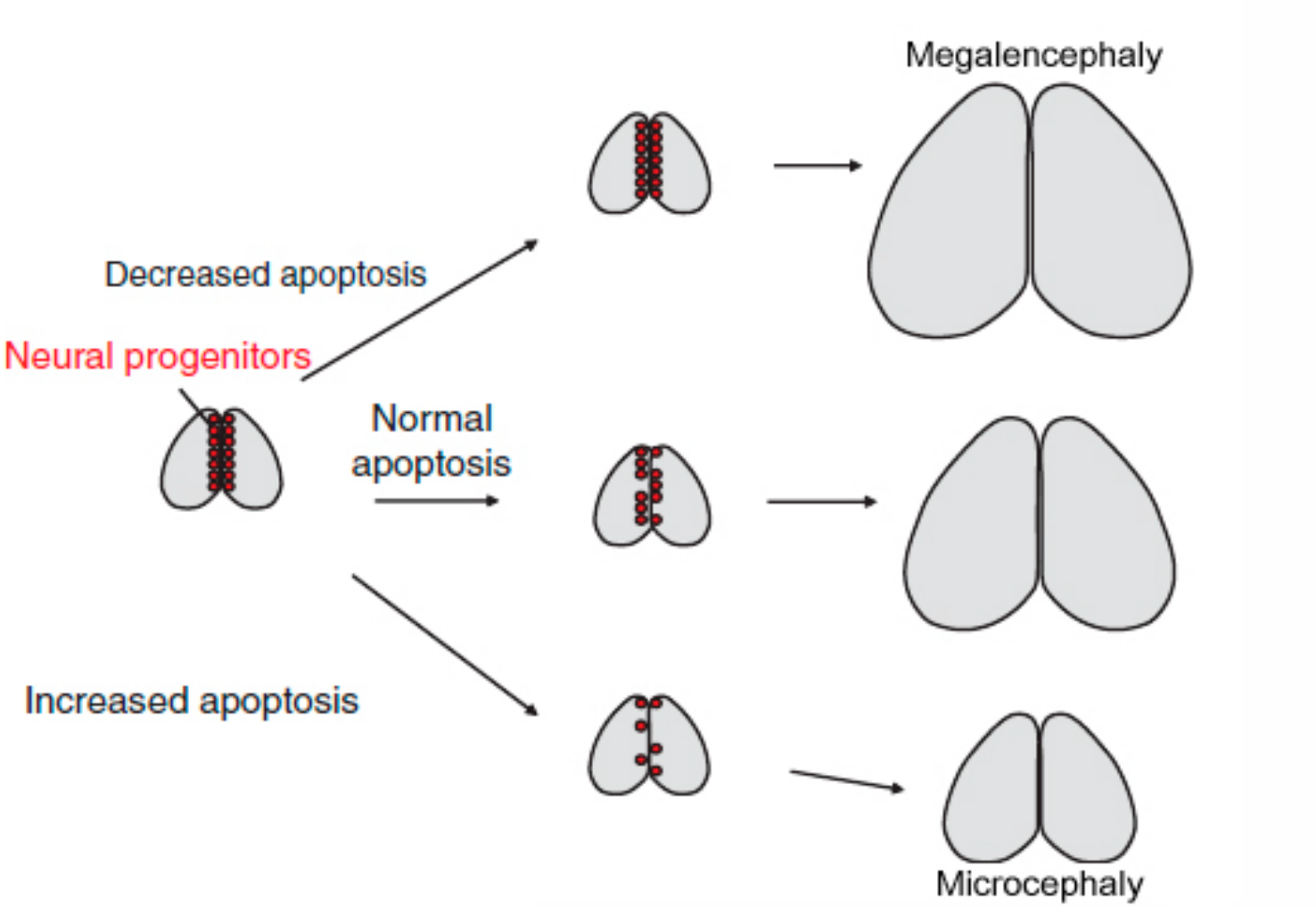
Bauer I. Crit Care. 2009;13(4):220


Birth
Prenatal
Postnatal
Infancy
Childhood
Adolescence
Proliferation
Migration
Apoptosis
Synaptogenesis
Myelination
Differentiation

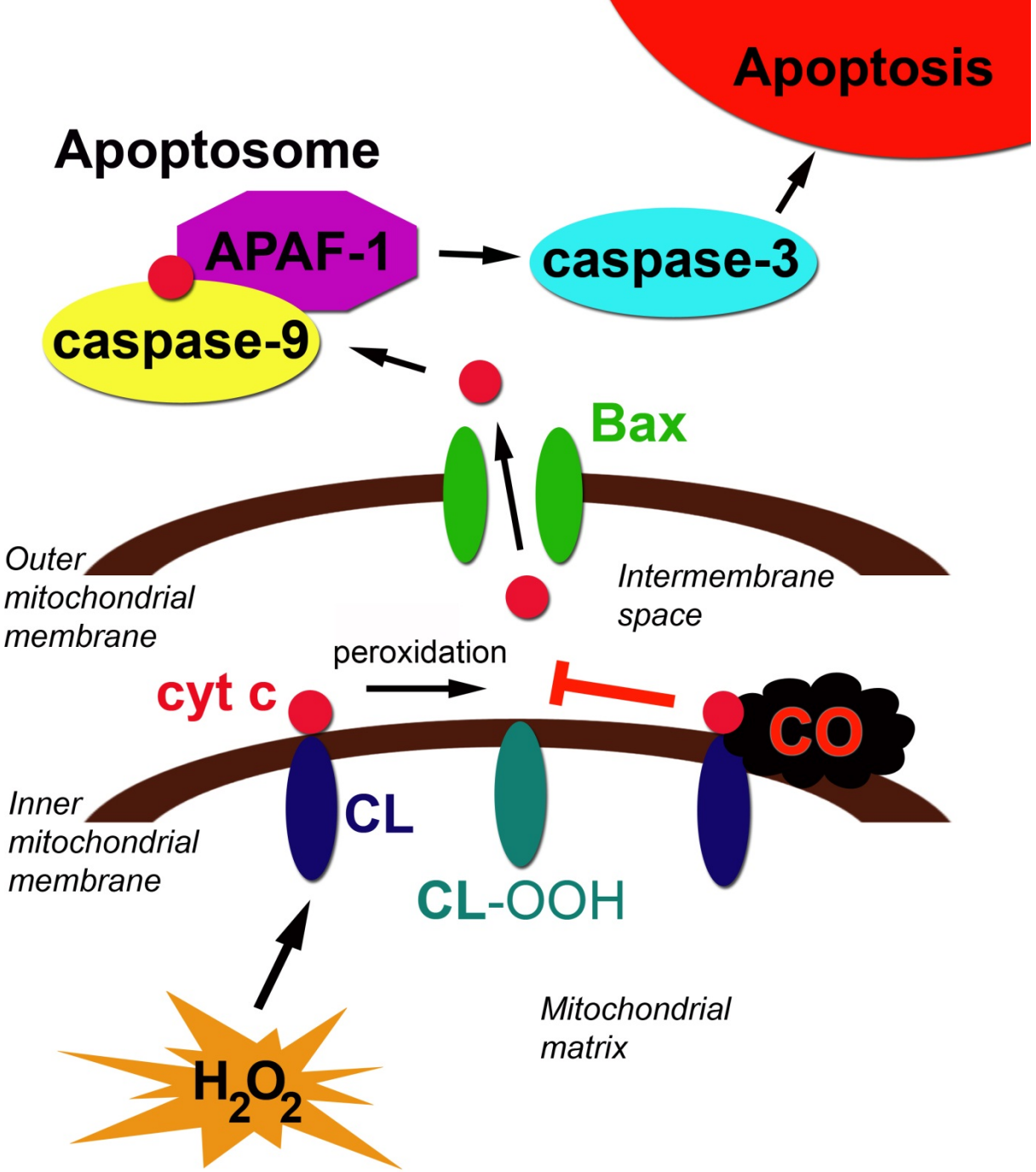
Neuronal death and patterning in the developing brain



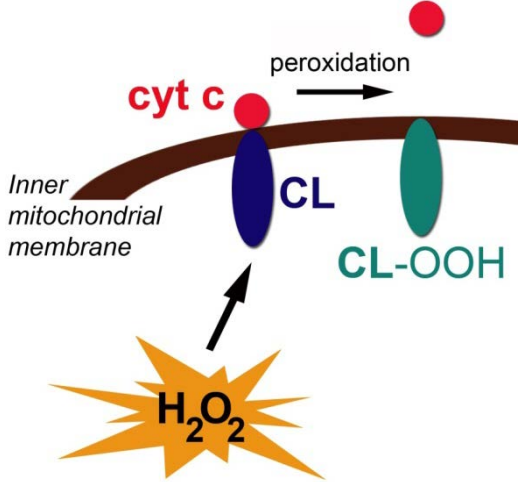
Vanderhaeghen P, Cheng HJ. Cold Spring Harb Perspect Biol. 2:a001859, 2010

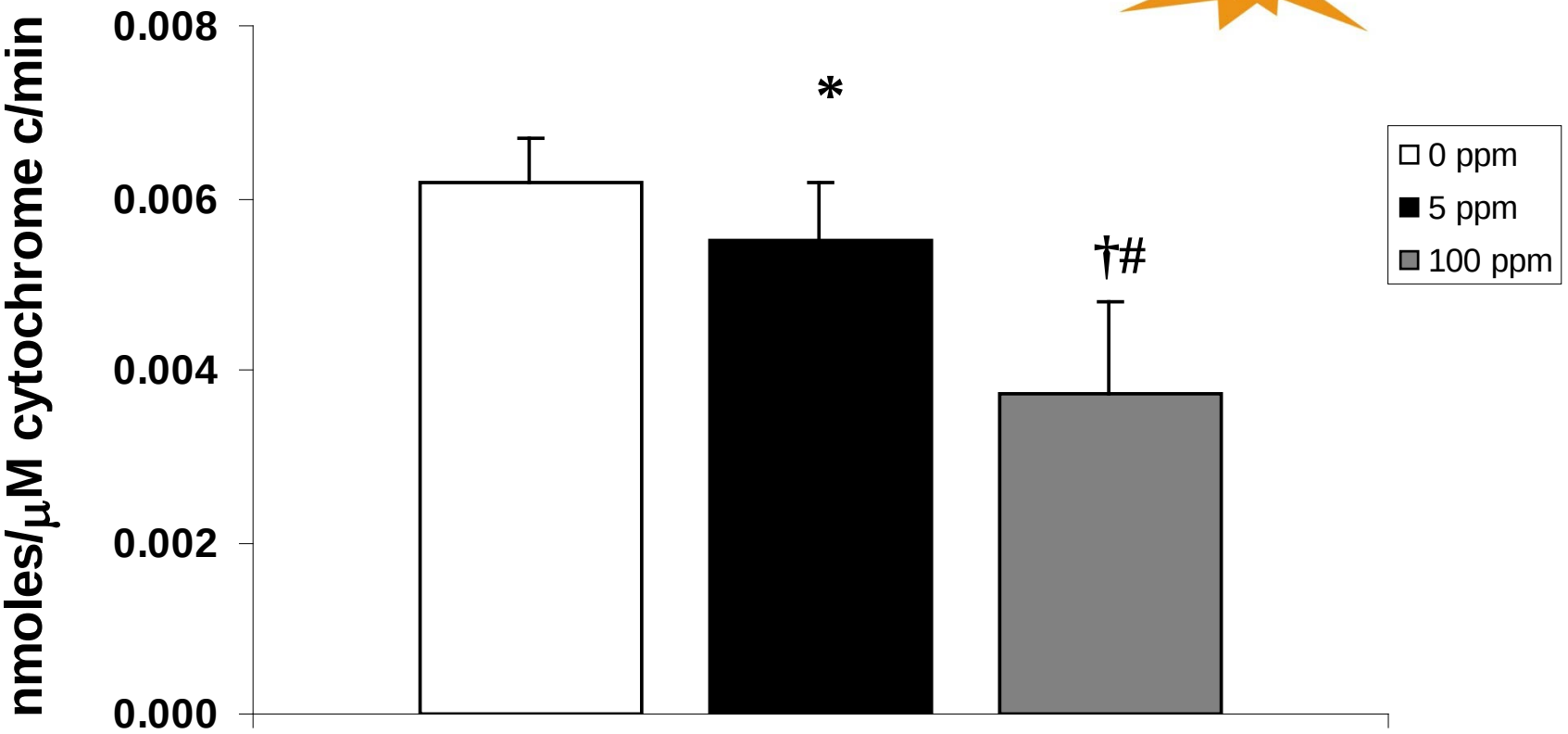


Vanderhaeghen P, Cheng HJ. Cold Spring Harb Perspect Biol. 2:a001859, 2010


Apoptosis
Apoptosome
APAF-1
caspase-3
caspase-9
Bax
Outer mitochondrial membrane
Intermembrane space
peroxidation
cyt c
CO
Inner mitochondrial membrane
CL
CL-OOH
H_2O_2
Mitochondrial matrix

Cytochrome c peroxidase activity

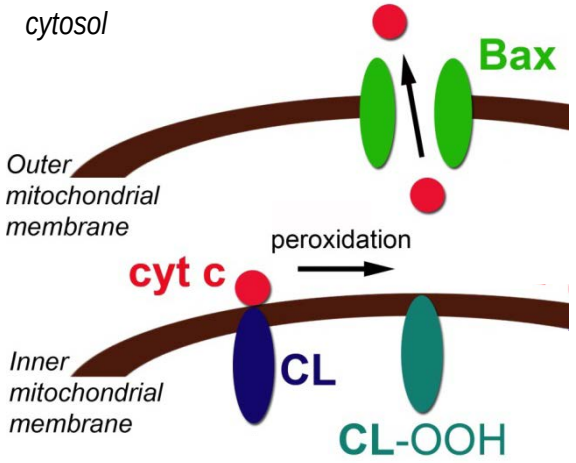


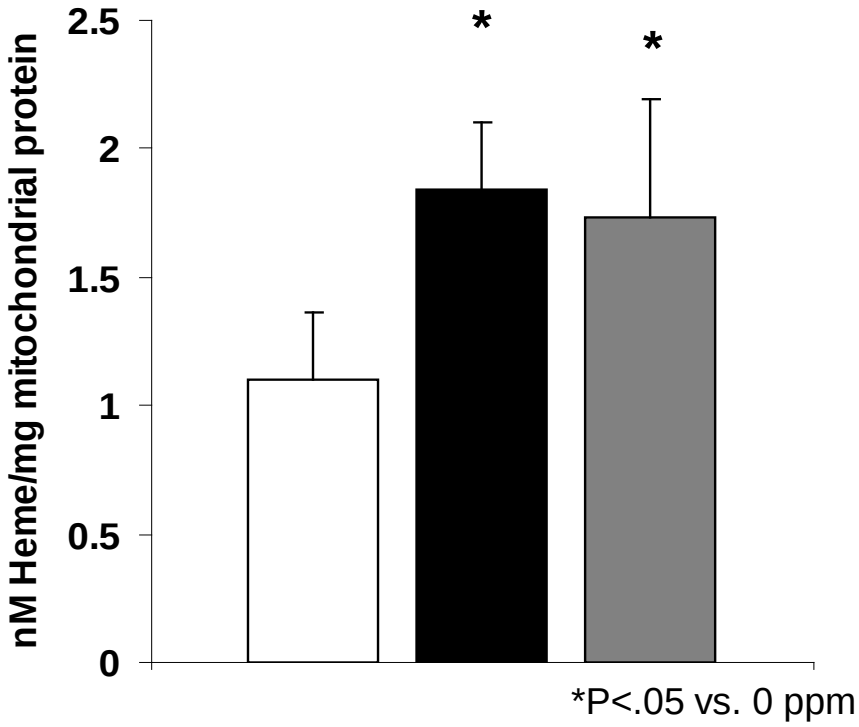


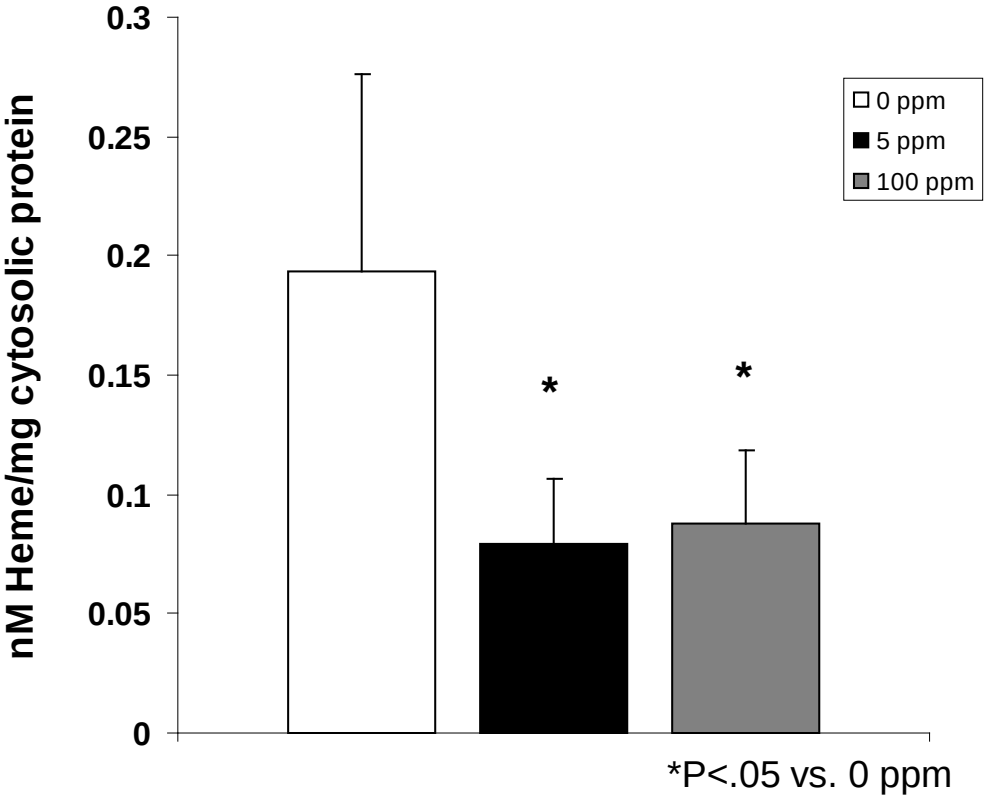
*P<.05 vs. 0 ppm
# P<.05 vs. 5 ppm
†P<.01 vs. 0 ppm

Cheng Y et al. PlosONE. 2012; 7:e32029

Cytochrome c release into cytosol







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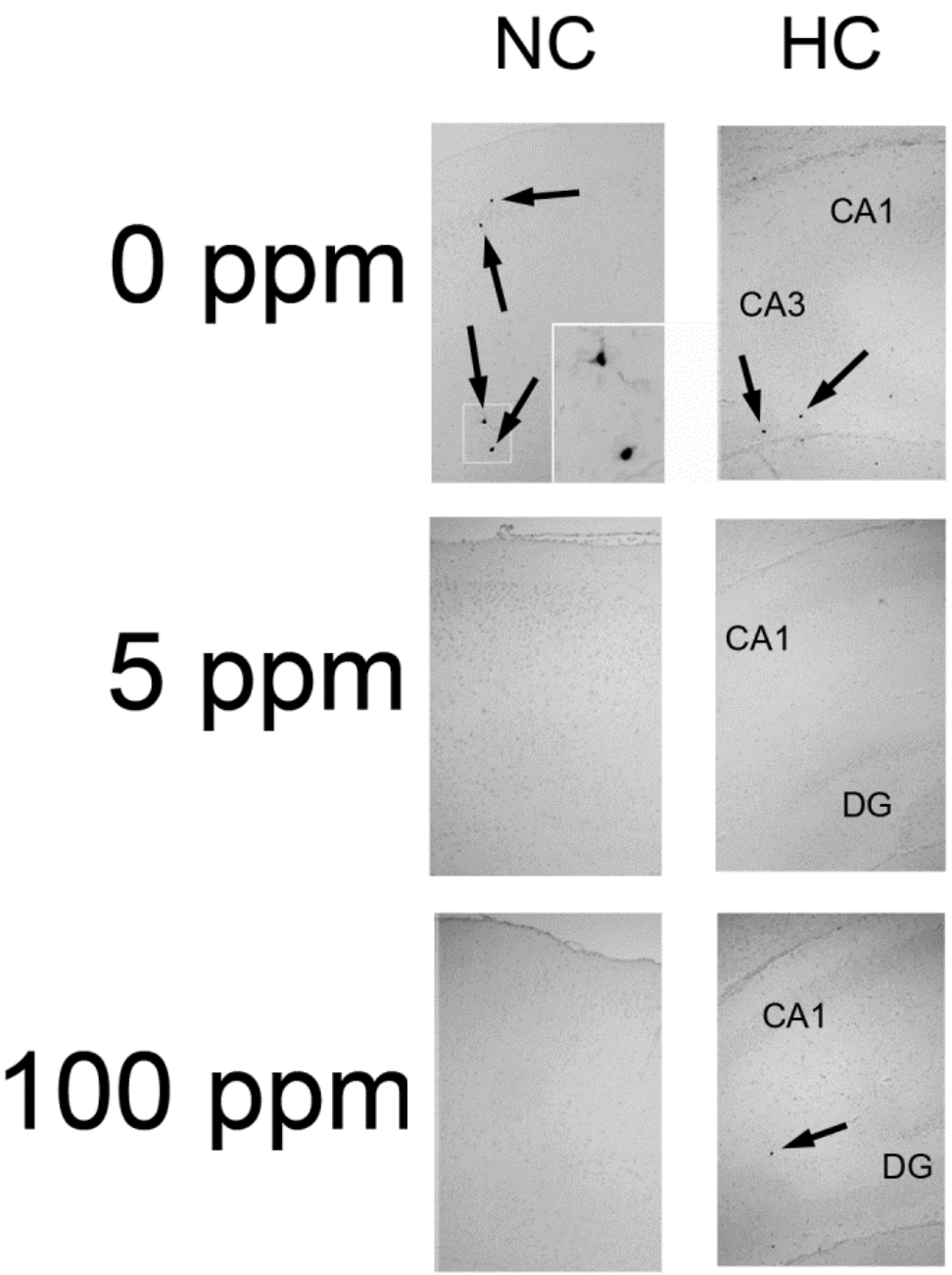
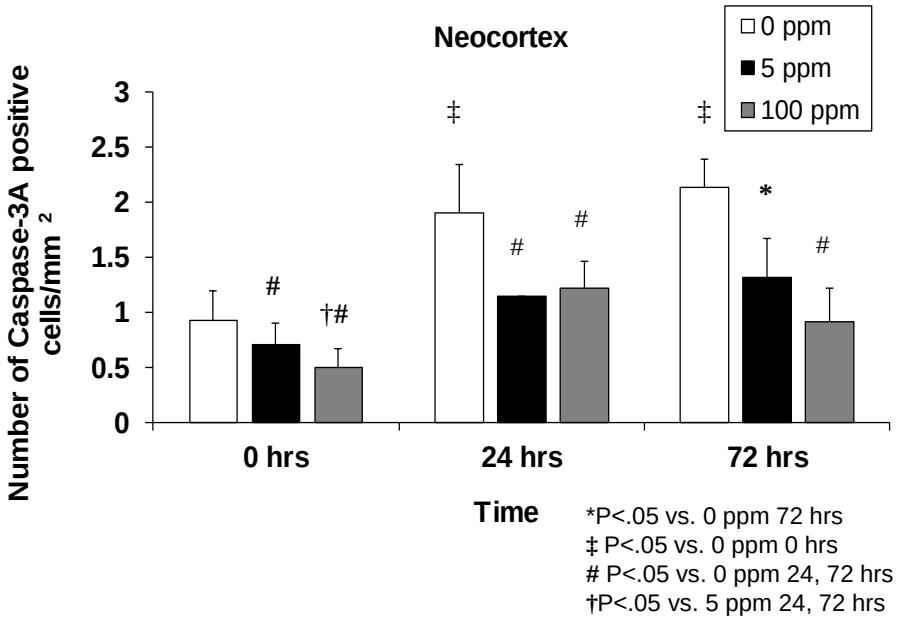
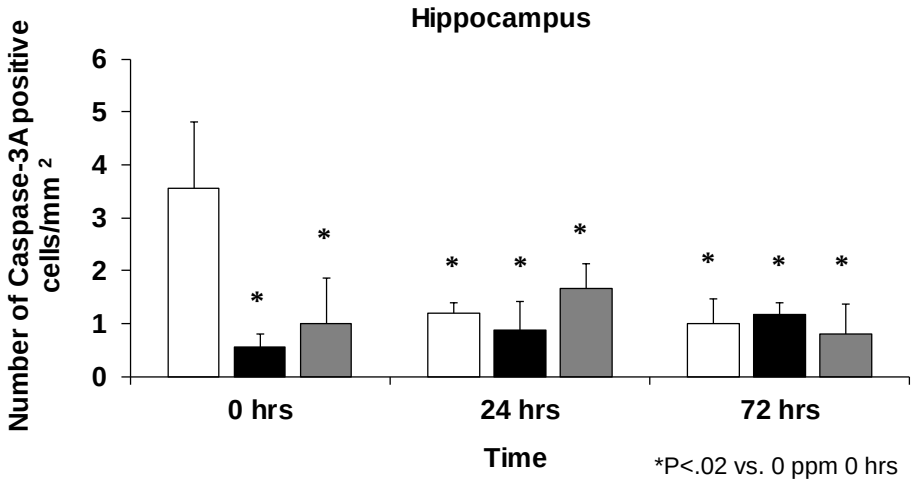
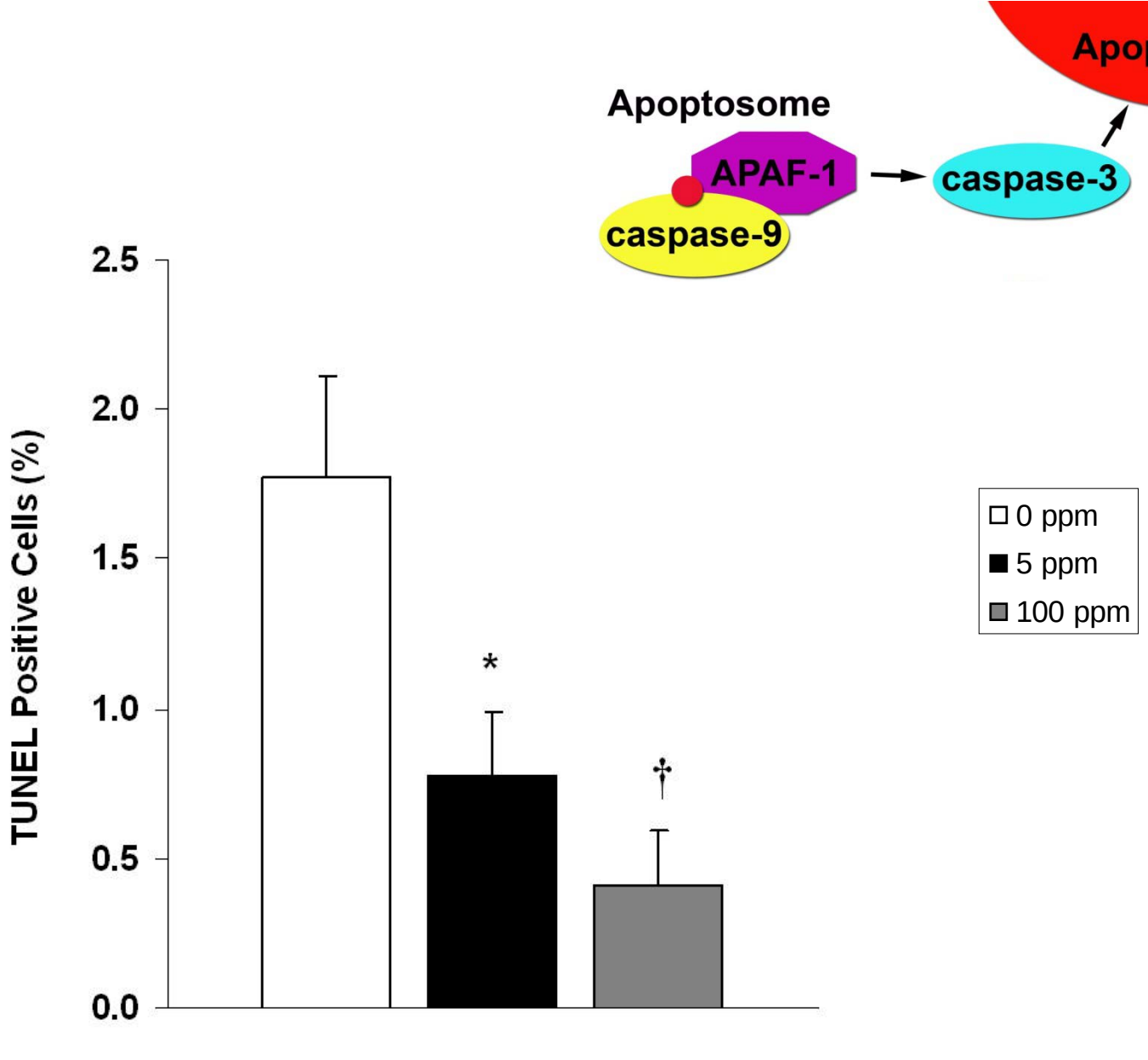






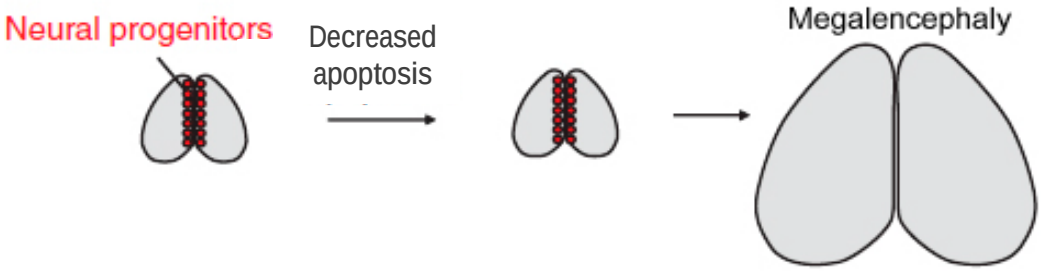
Cheng Y et al. PlosONE. 2012; 7:e32029

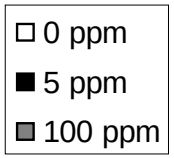


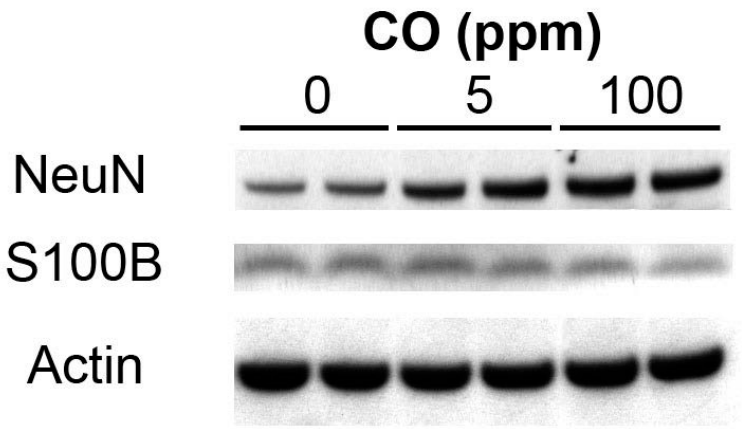
*P<.05 vs. 0 ppm

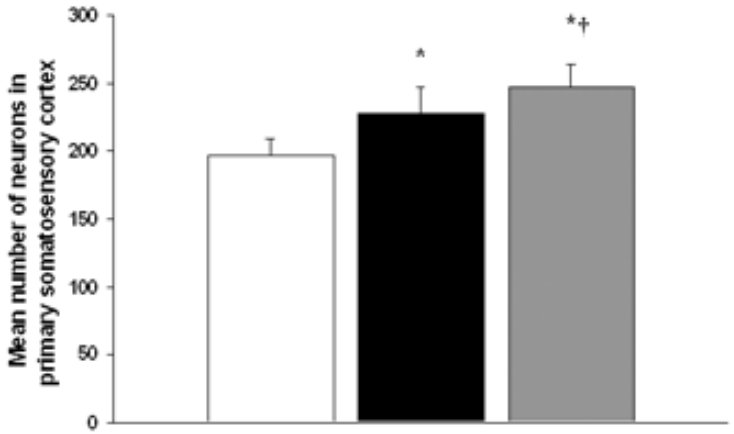
†P<.02 vs. 0 ppm

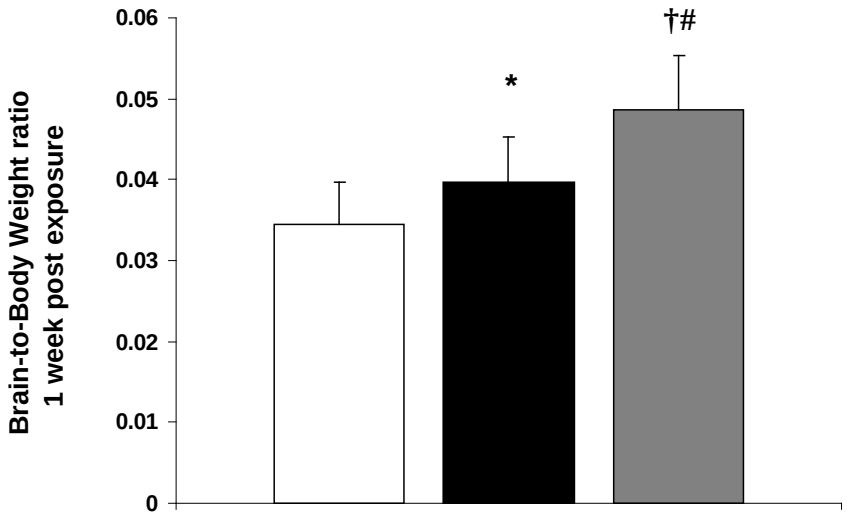
Cheng Y et al. PlosONE. 2012; 7:e32029

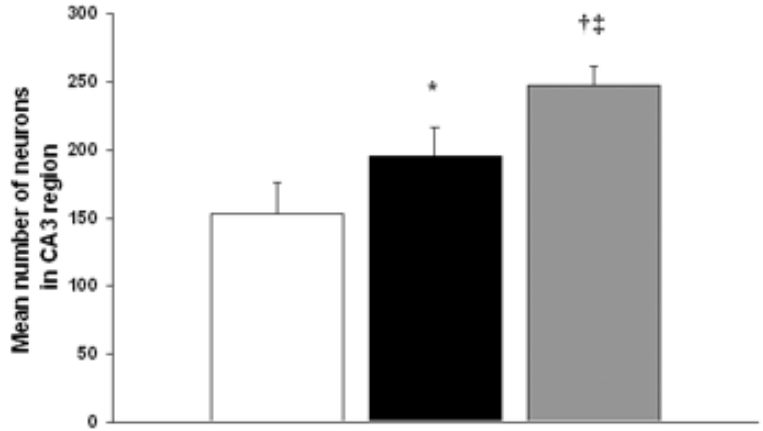








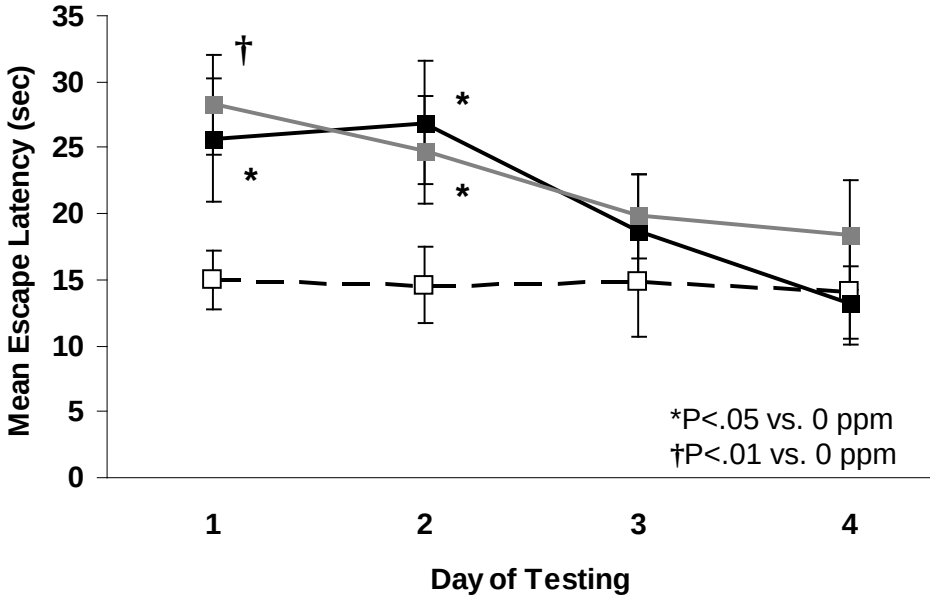




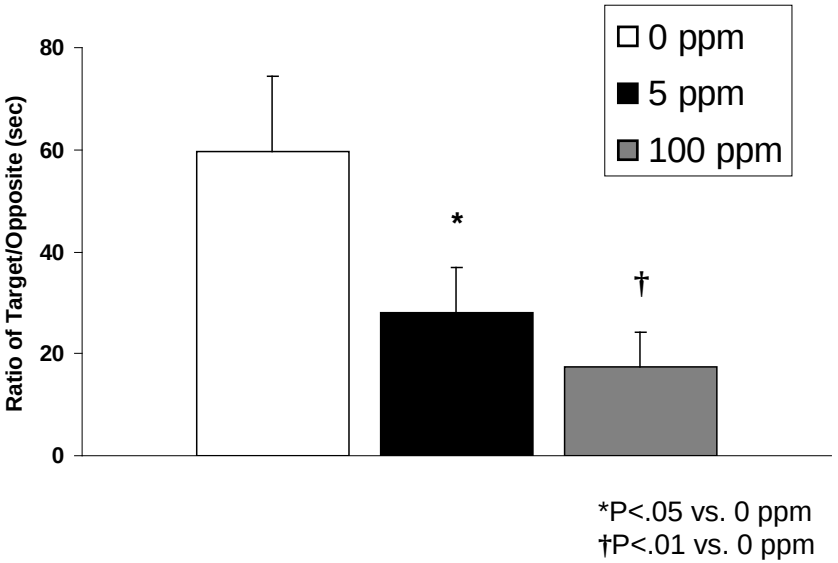
*P<.05 vs. 0 ppm
# P<.05 vs. 5 ppm
†P<.01 vs. 0 ppm

Cheng Y et al. PlosONE. 2012; 7:e32029

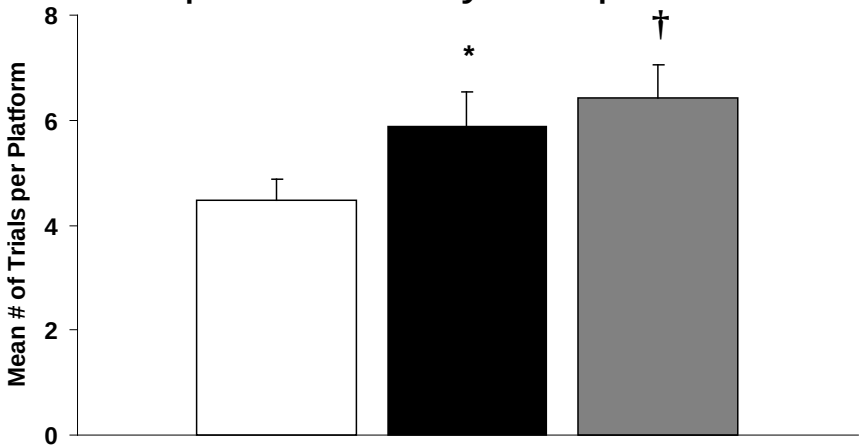
Reference memory is impaired



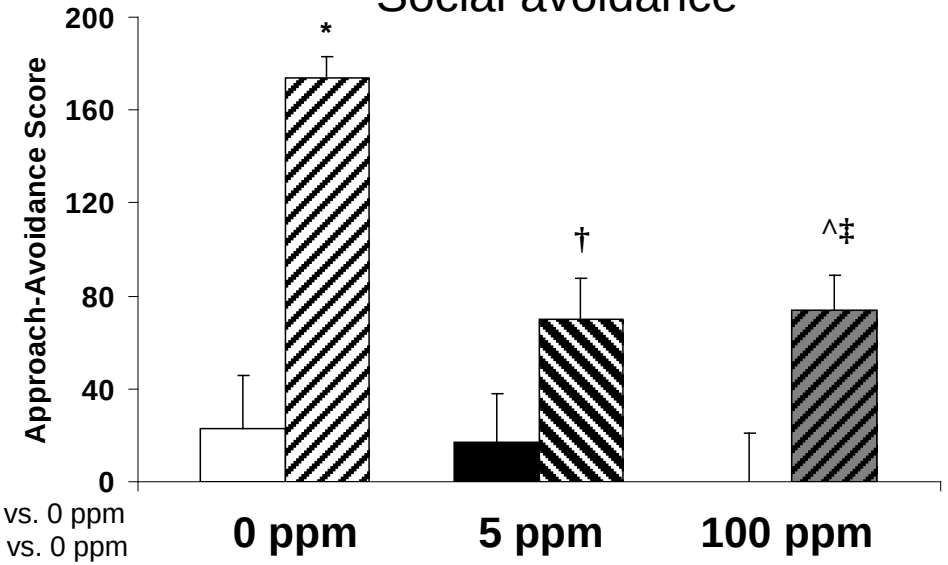
Memory retention is impaired



Spatial memory is impaired

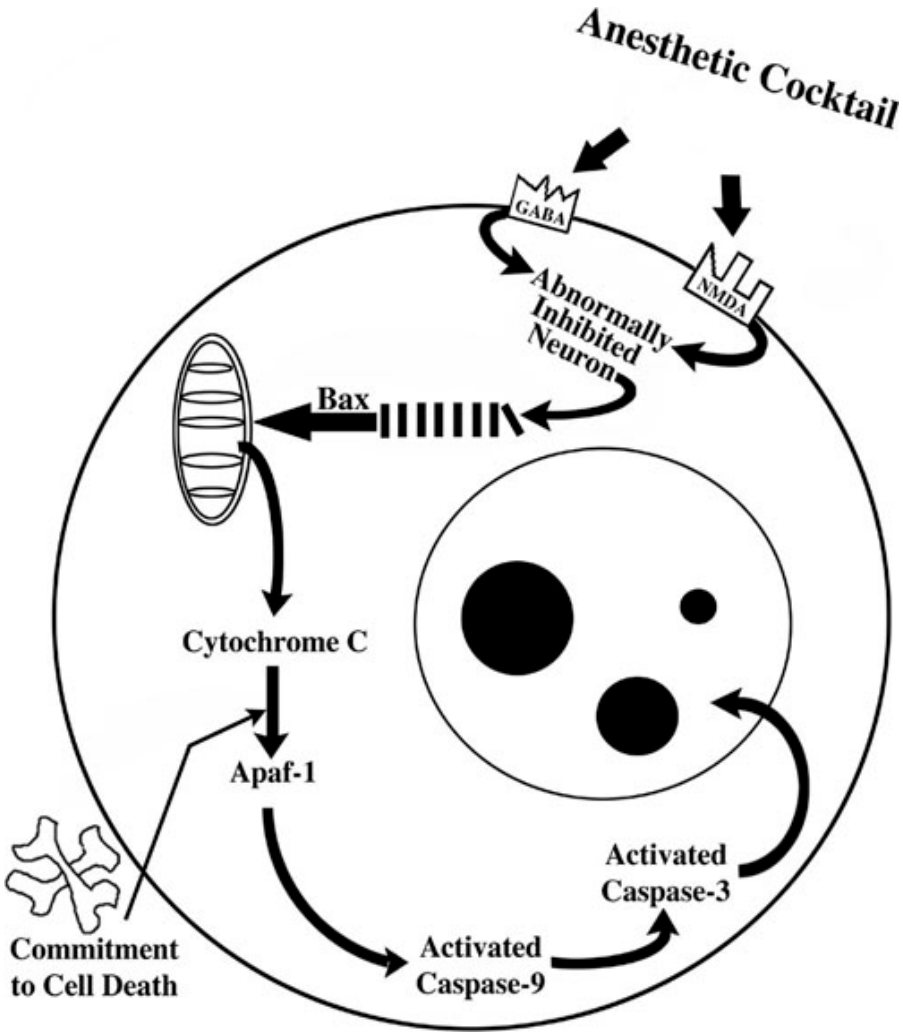


Social avoidance



Cheng Y et al. PlosONE. 2012; 7:e32029

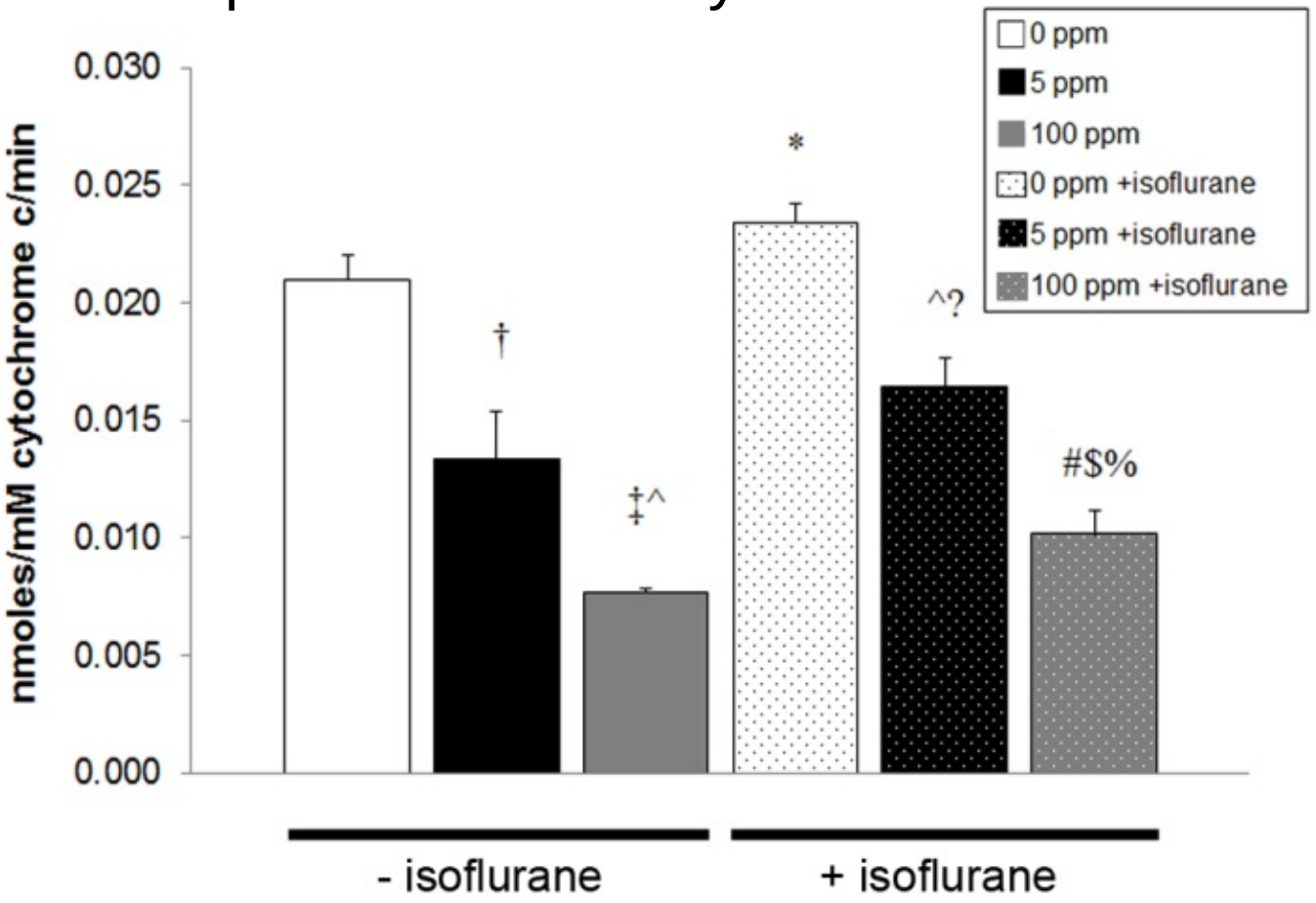
Mechanism of anesthesia-induced neurotoxicity

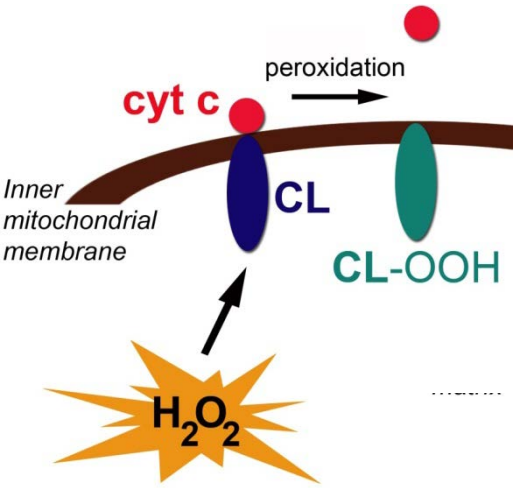


Olney JW, et al. Anesthesiology. 101:273-5, 2004.

Can inspired CO prevent anesthesia-induced neuronal apoptosis in the developing brain?

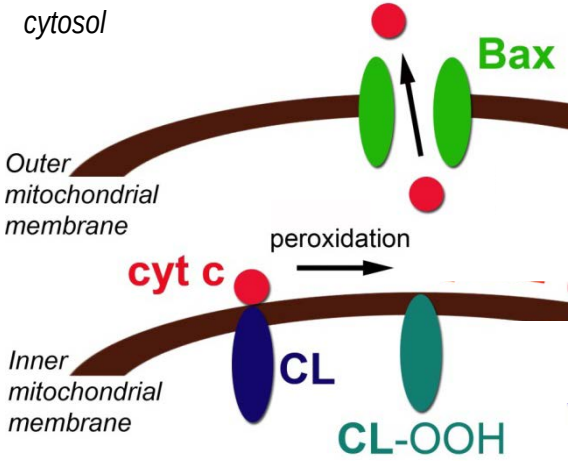
Cytochrome c peroxidase activity

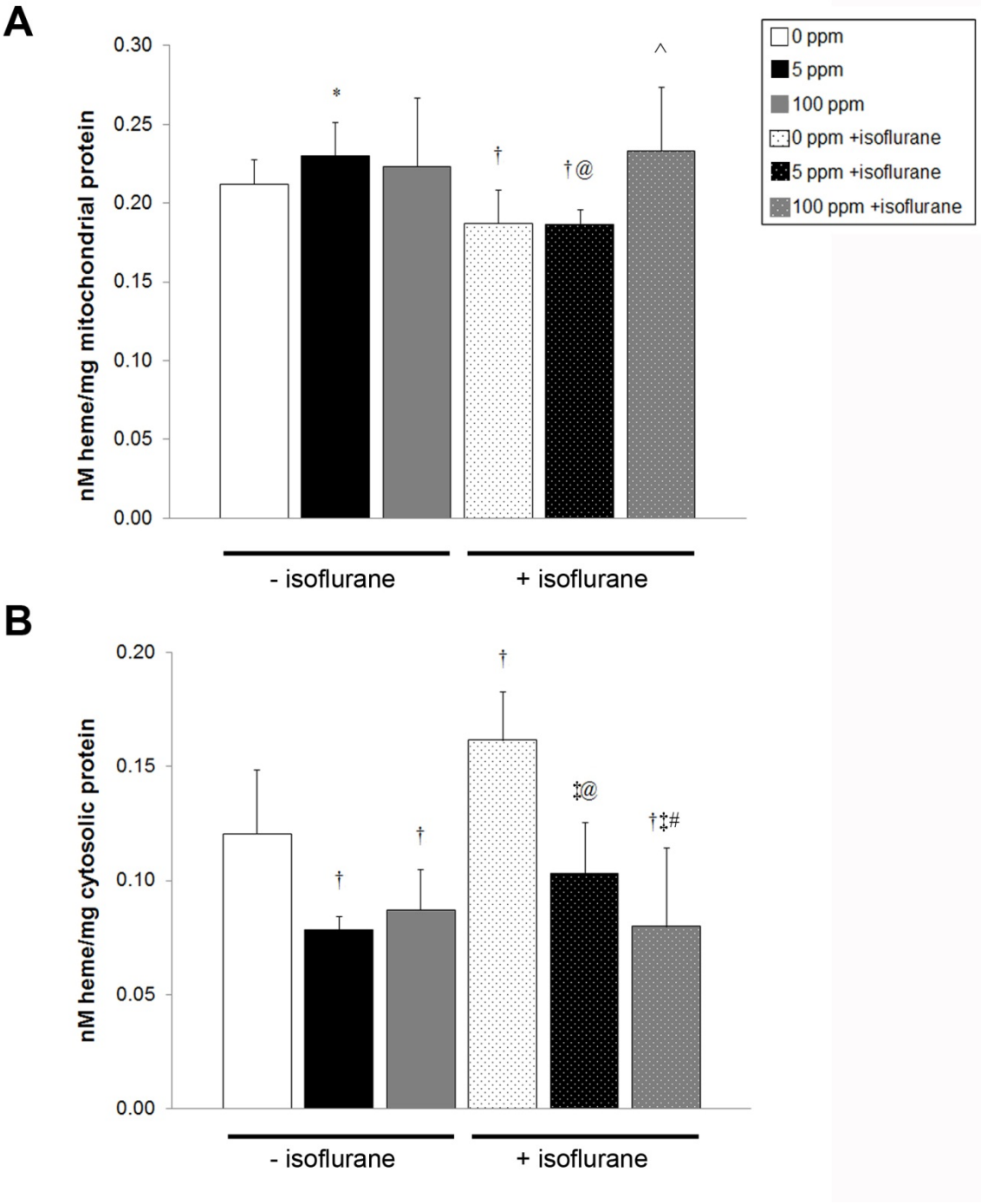




*P < .05 vs. 0 ppm CO –isoflurane, P < .001 vs. 5 ppm CO –isoflurane, vs. 100 ppm CO – isoflurane. †P < .01 vs. 0 ppm CO -isoflurane. ‡P < .001 vs. 0 ppm CO –isoflurane. ^P < .05 vs. 5 ppm CO –isoflurane. @P < .01 vs. 5 ppm CO –isoflurane. #P < .05 vs. 100 ppm CO – isoflurane. ?P < .01 vs. 0 ppm CO +isoflurane. $$P$ < .01 vs. 5 ppm CO +isoflurane. %P < .001 vs. 0 ppm CO +isoflurane.

Cheng Y and Levy RJ. Anes Analg 2014; 118(6):1284-92





*P < .05 vs. 0 ppm CO –isoflurane. †P < .01 vs. 0 ppm CO –isoflurane. #P < .05 vs. 5 ppm CO +isoflurane. ‡P < .001 vs. 0 ppm CO –isoflurane. ^P < .01 vs. 0 ppm CO and 5 ppm +isoflurane. @P < .01 vs. 5 ppm CO –isoflurane.

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Activated caspase-3

Isoflurane

NC HC H/T

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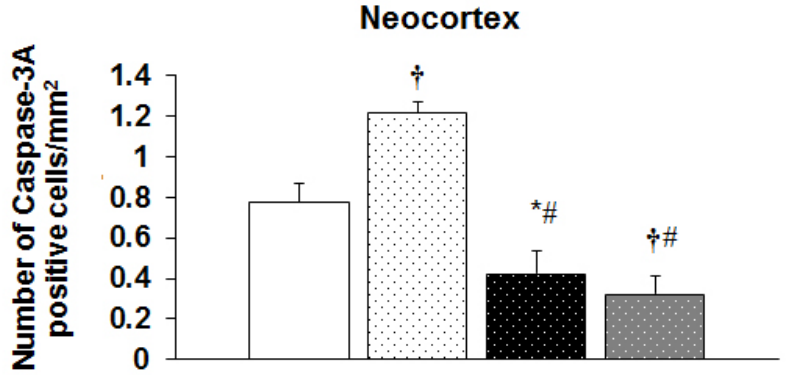

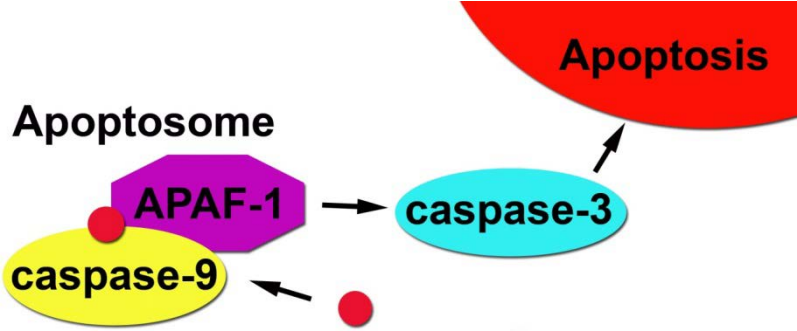

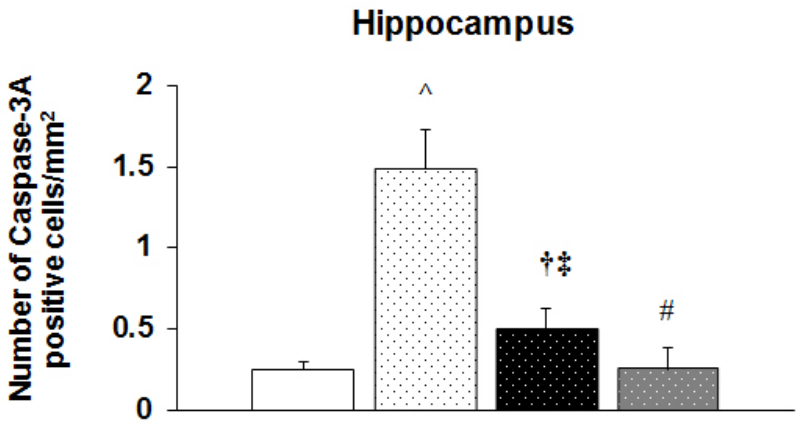

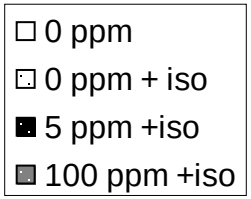

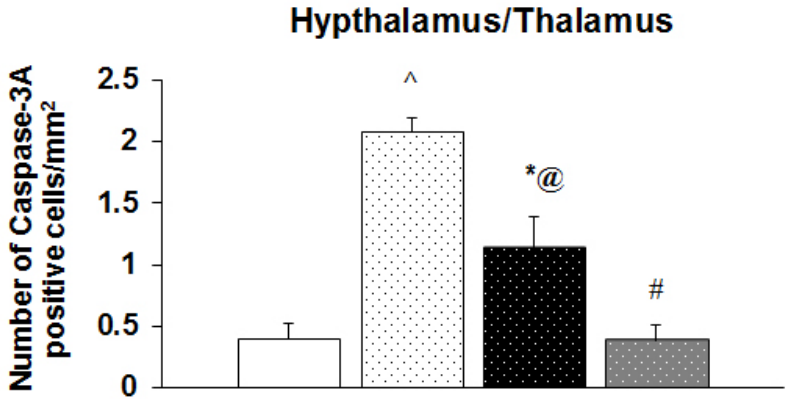

*P < .05 vs. 0 ppm CO -isoflurane. †P < .01 vs. 0 ppm CO -isoflurane. ^P < .001 vs. 0 ppm CO –isoflurane. @ P < .05 vs. 0 ppm CO +isoflurane. ‡P < .01 vs. 0 ppm CO +isoflurane. # P < .001 vs. 0 ppm CO +isoflurane. $$P$ < .05 vs. 5 ppm CO +isoflurane.

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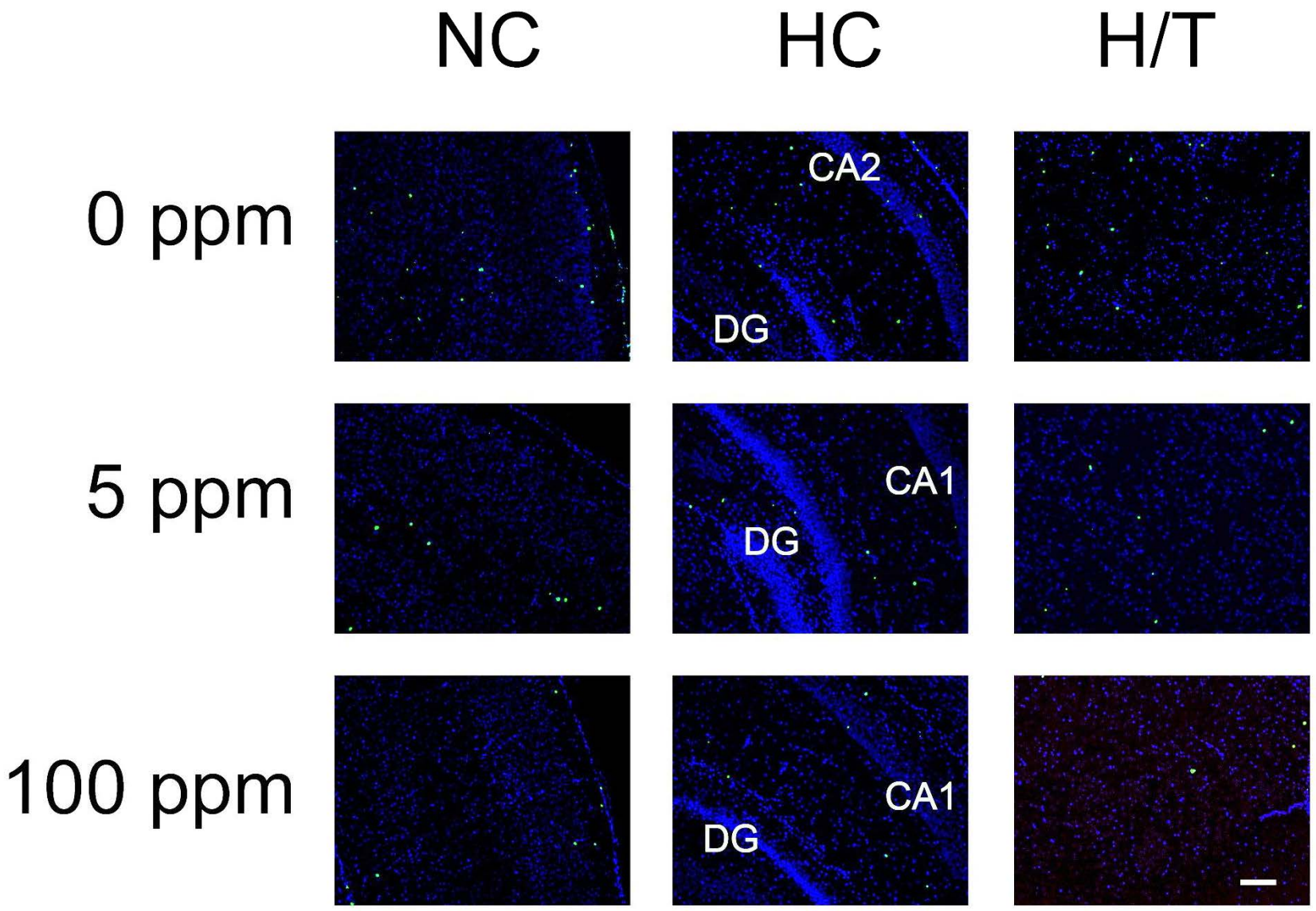
TUNEL

Isoflurane



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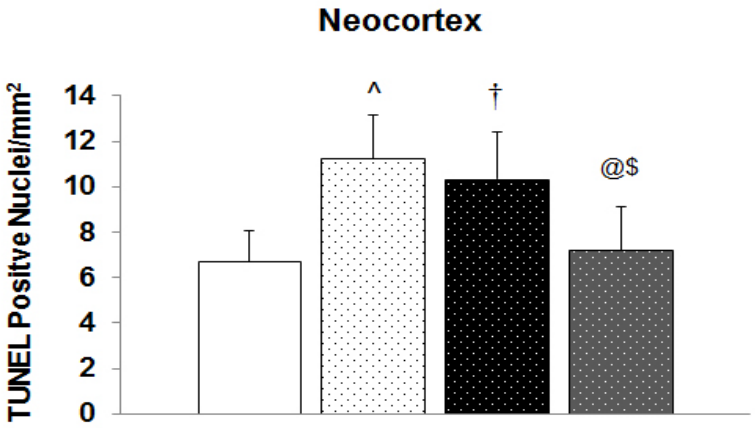

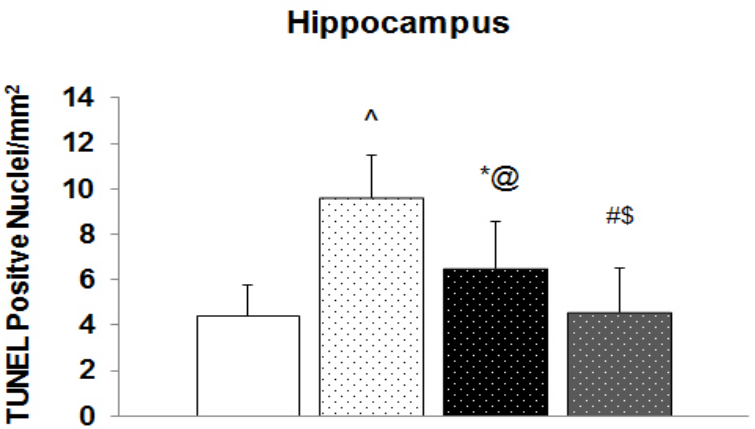

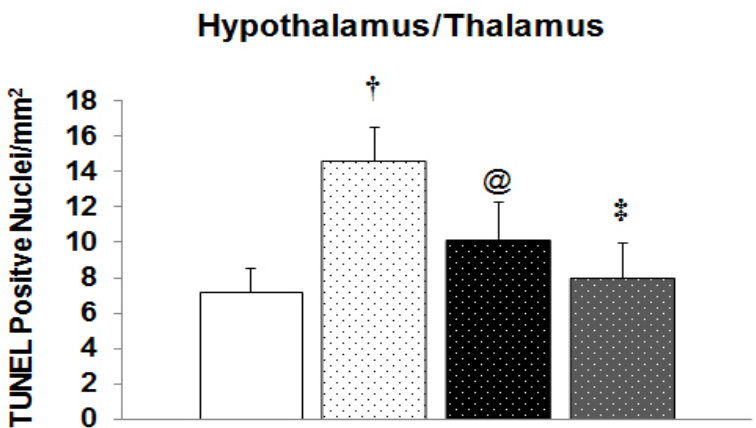

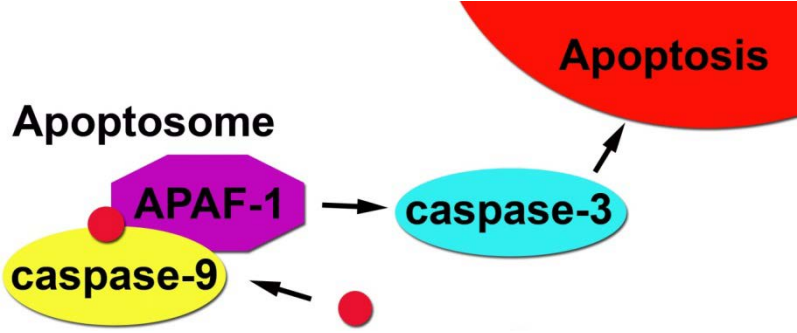

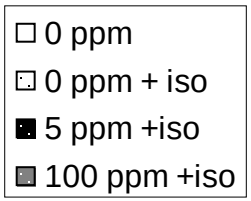

*P < .05 vs. 0 ppm CO -isoflurane.
†P < .01 vs. 0 ppm CO -isoflurane.
^P < .001 vs. 0 ppm CO –isoflurane. @ P < .05 vs. 0 ppm CO +isoflurane. ‡P < .01 vs. 0 ppm CO +isoflurane.
% P < .05 vs. 5 ppm CO –isoflurane. &P < .01 vs. 5 ppm CO –isoflurane.
$$P$ < .05 vs. 5 ppm CO +isoflurane.
?P < .05 vs. 100 ppm CO –isoflurane.

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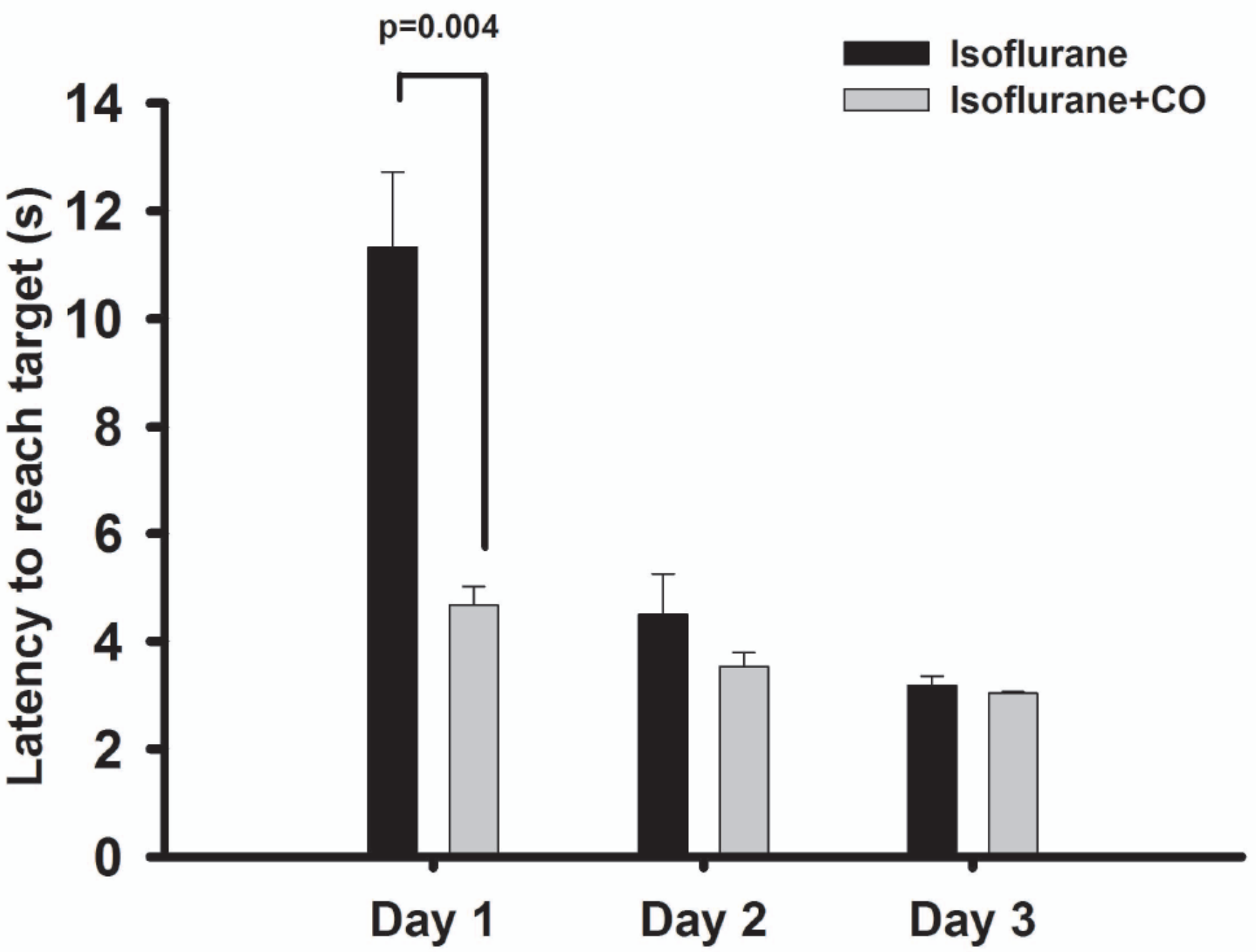
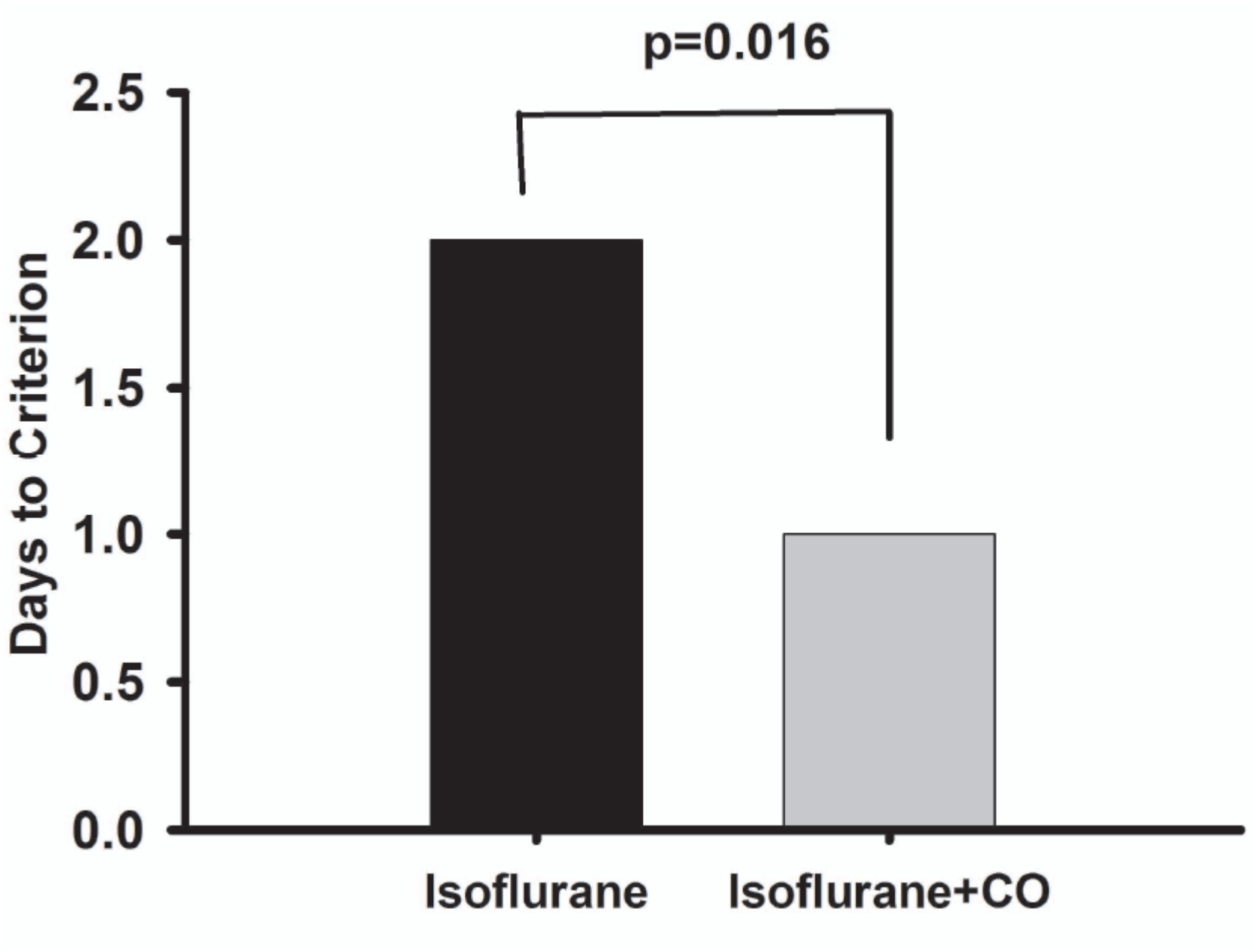

p=0.004
Isoflurane
Isoflurane+CO
Latency to reach target (s)
0
2
4
6
8
10
12
14
Day 1
Day 2
Day 3


p=0.016
2.5
2.0
1.5
1.0
0.5
0.0
Days to Criterion
Isoflurane
Isoflurane+CO

Inspired CO may limit and prevent isoflurane-induced neuronal apoptosis in the developing brain and may prevent anesthesia-mediated effects on memory and learning

PANDA cohort (Sun LS, et. al.)

10 patients underwent general inhalational anesthesia for urologic surgery

Identified with detailed OR records

FGF (oxygen, nitrous oxide, air)

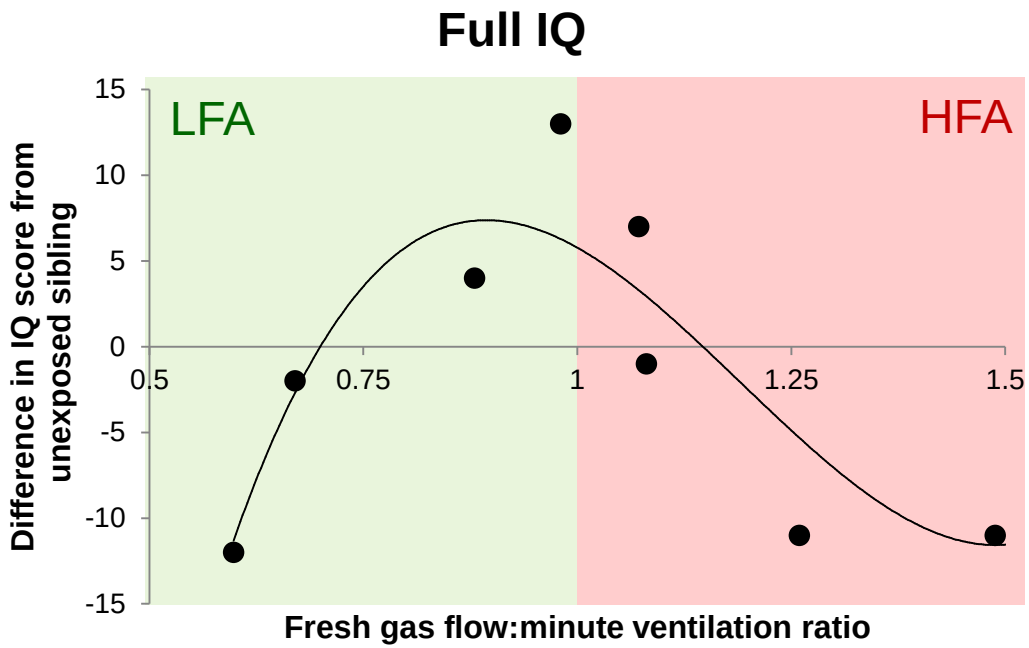
TV, RR (minute ventilation)

9 males, 1 female

5 mo – 2 years of age

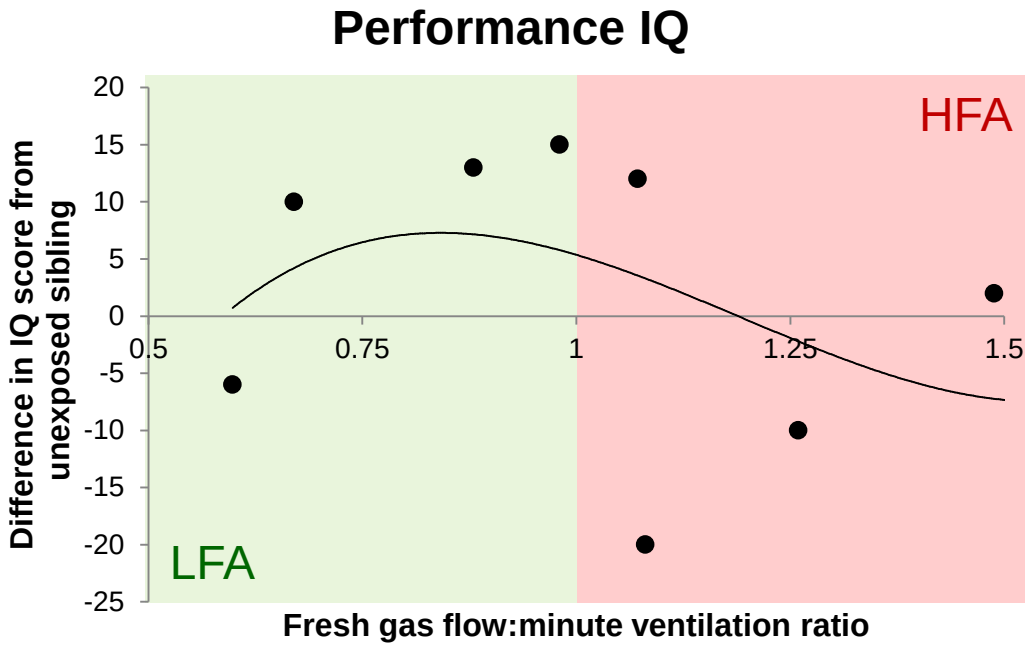
6.9 – 13.6 kg

IQ difference from sibling related to FGF:Ve



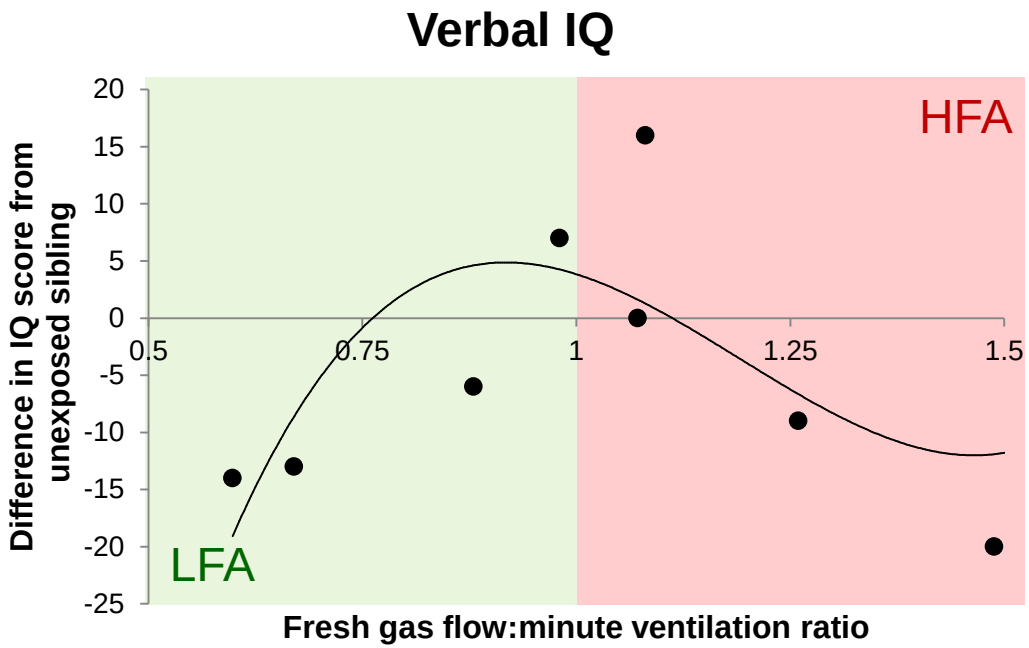
† $P<.01$
$r = 0.82$

IQ difference from sibling related to FGF:Ve



r = 0.41

IQ difference from sibling related to FGF:Ve

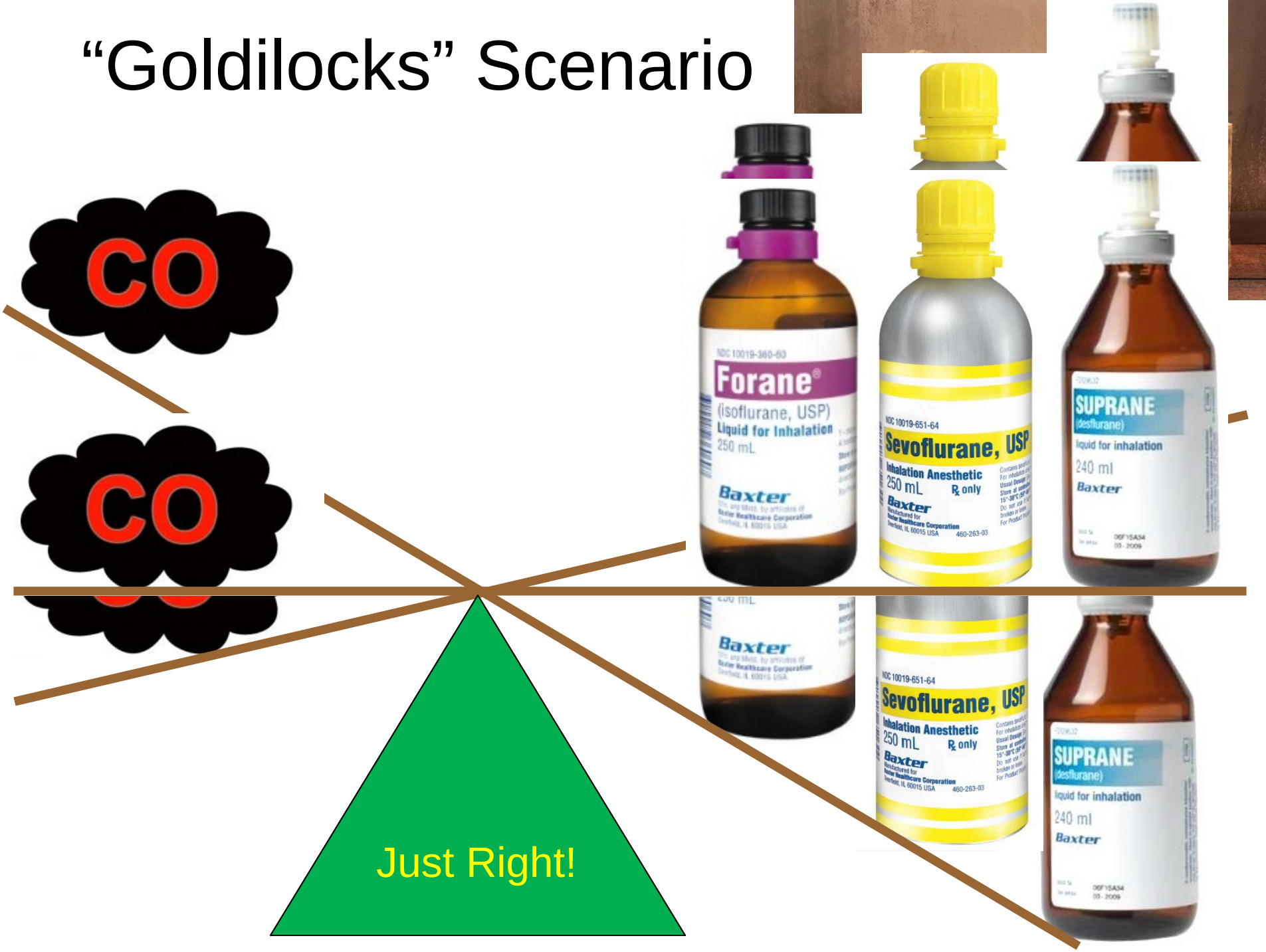


* *P*<.05

r = 0.74

Low-flow anesthesia targeting mild CO-rebreathing and subclinical CO exposure may prevent and inhibit anesthesia-induced neurotoxicity

“Goldilocks” Scenario



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