INTERPLAY OF ROS AND MITOCHONDRIAL CALCIUM IN THE MECHANISM OF CO TOXICITY IN HUMAN NEURONS

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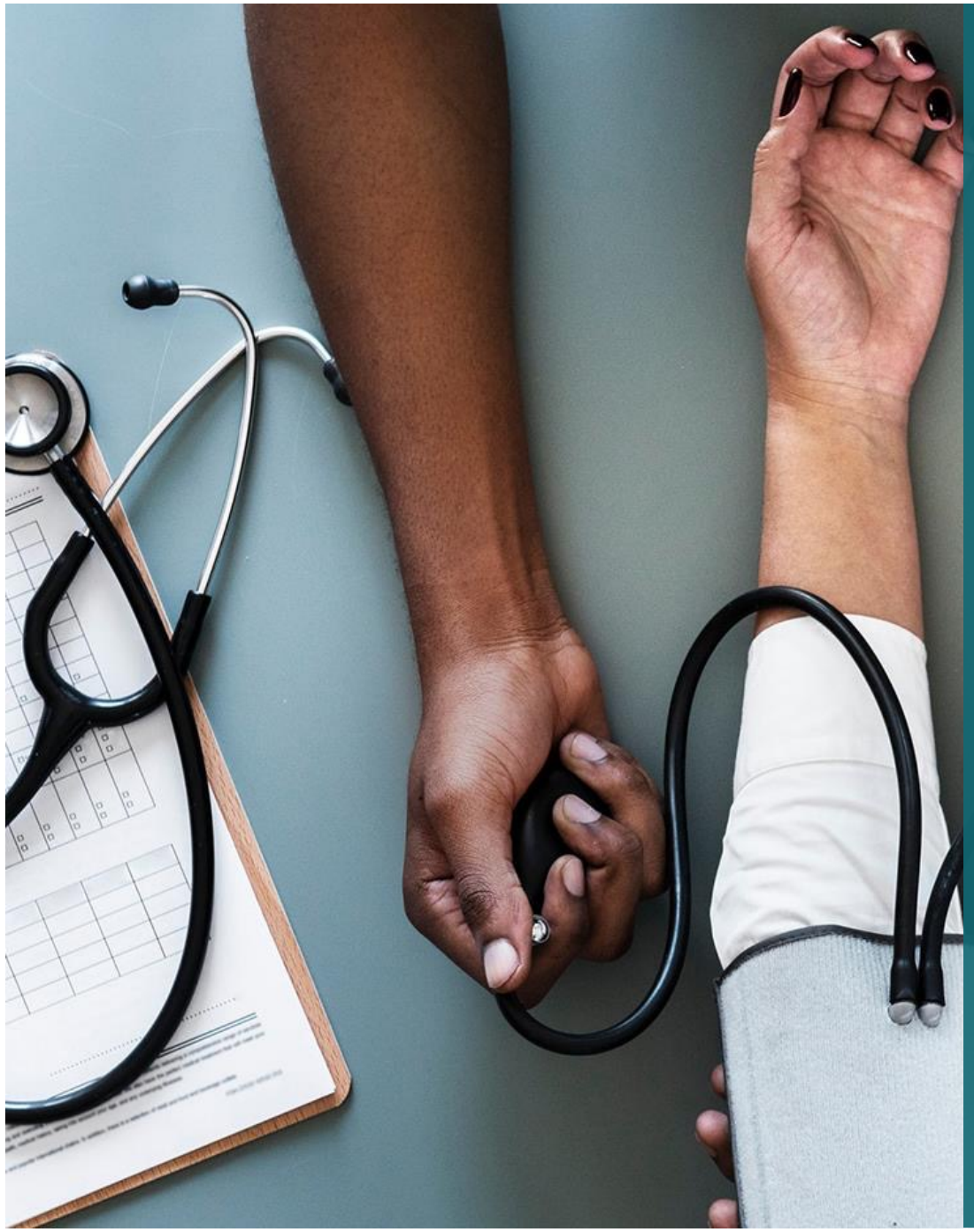

THE PROBLEM

Delayed neurological or psychiatric sequelae (DNS) occur in up to 67% of survivors of CO poisoning

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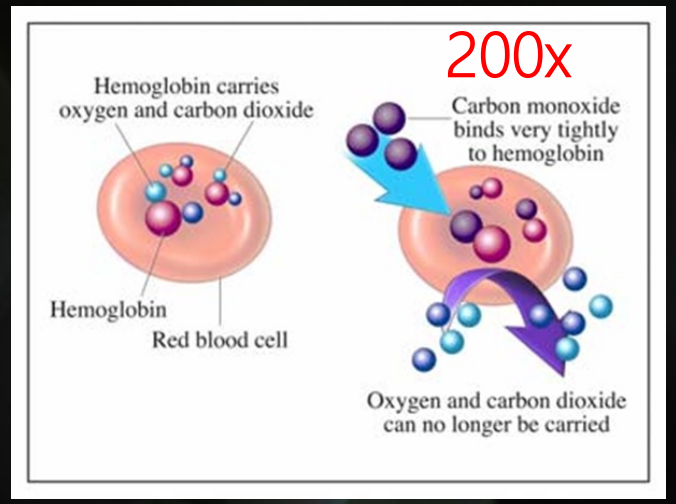
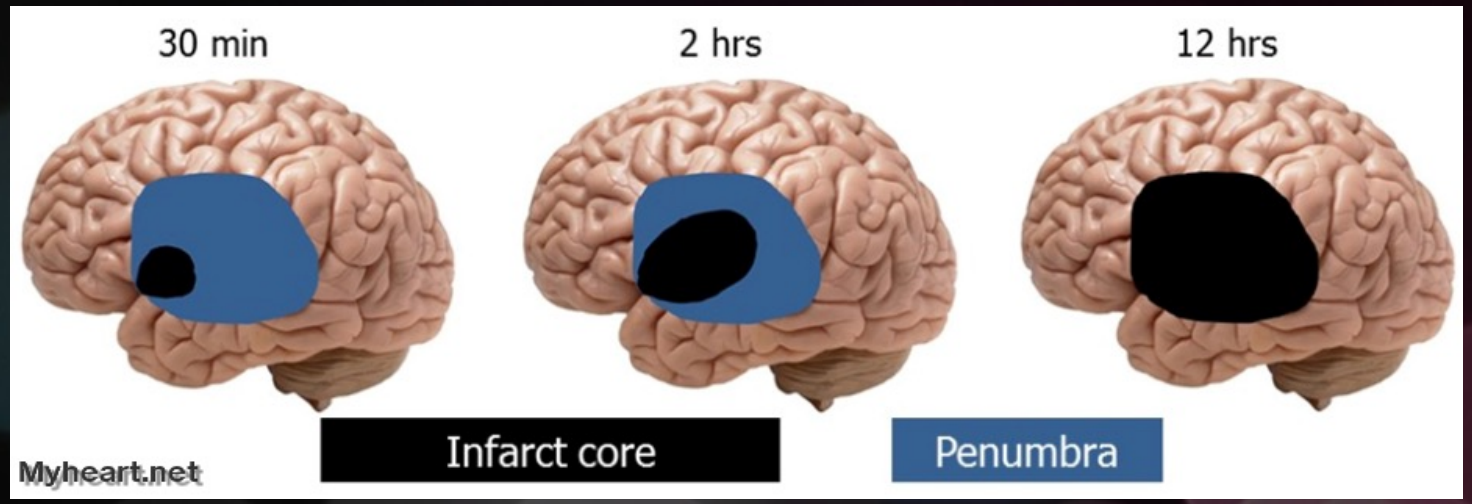
CO leads to hypoxia by the formation of carboxyhaemoglobin, preventing normal oxygen delivery to the tissue.





"...zone with functional impairment but with morphologic integrity, which has the capacity to recover if perfusion is performed..."

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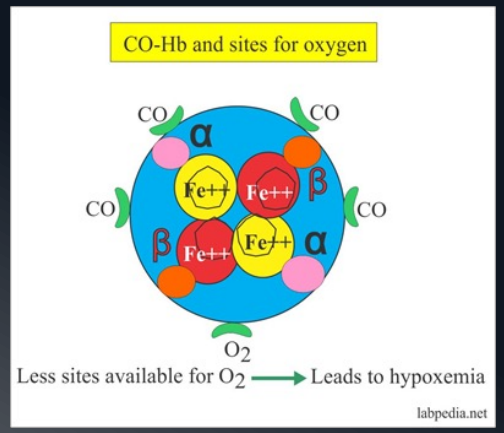
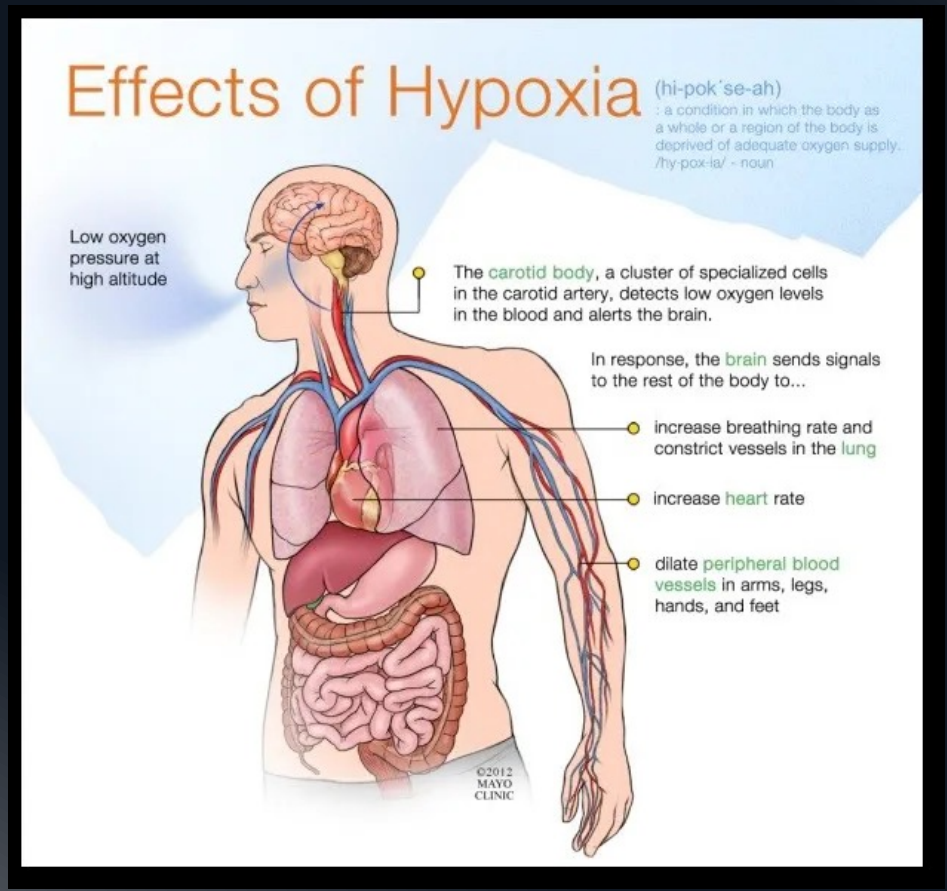
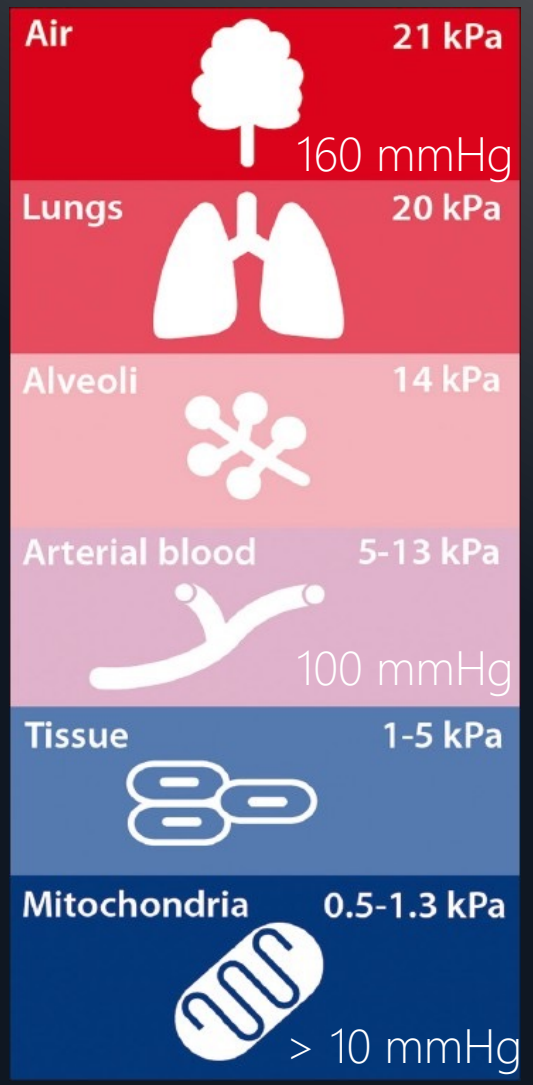
CO poisoning = generalized hypoxia/anoxia?







CO inhibits oxygen-dependent processes and mitochondrial respiration is blocked in the absence of oxygen.

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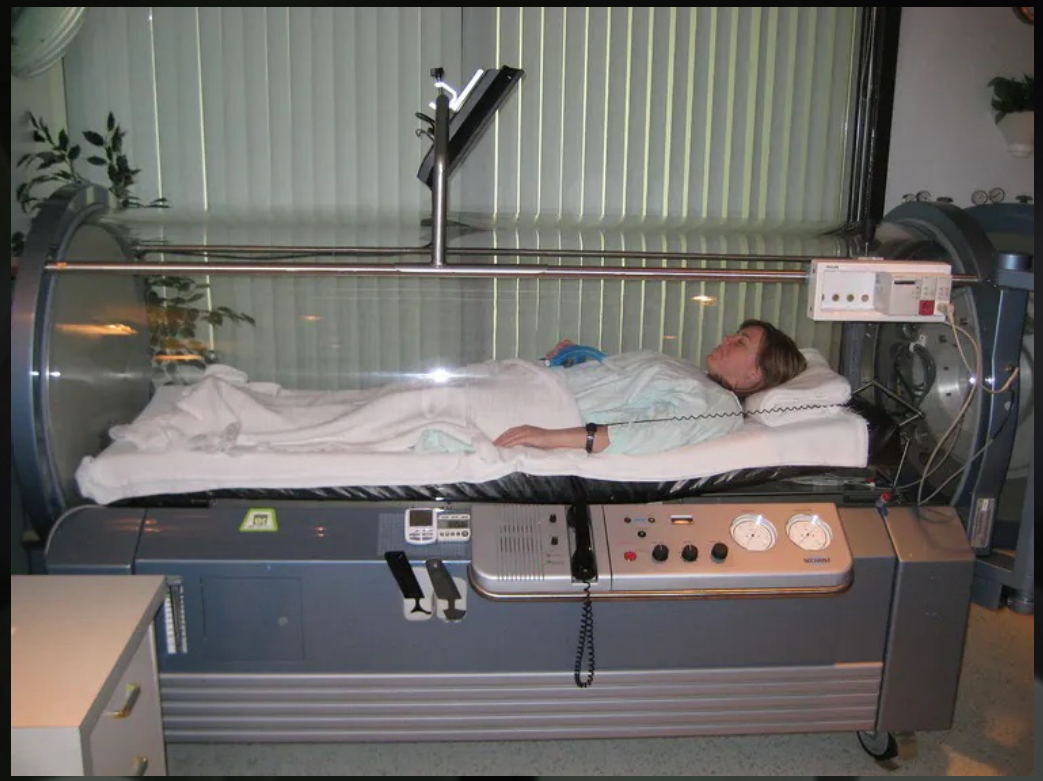
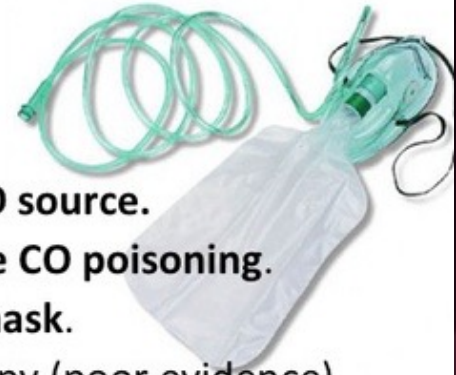


Management



- **Immediate removal from CO source.**
- **Smoke inhalation → assume CO poisoning.**
- **100% O_2** via **non-breather mask.**
  +/- Hyperbaric oxygen therapy (poor evidence).
- **Repeated ABG to monitor.**
- Treat any metabolic acidosis (lactic acid).

- **Low levels (<10%) → admission not needed** *
  * Unless pregnant / extreme age / anaemia or CVD.

First line treatment of patients with CO-poisoning is 100% high flow or hyperbaric oxygen application.

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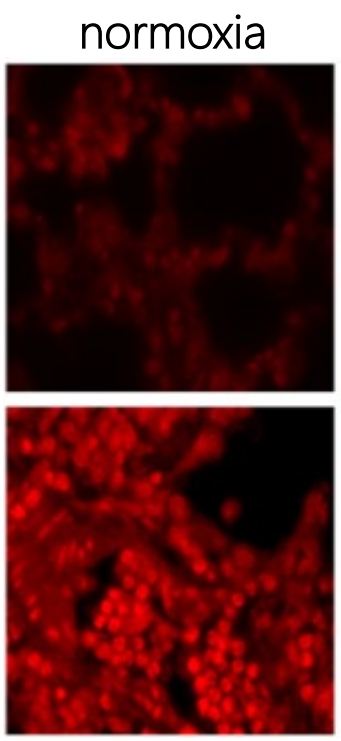
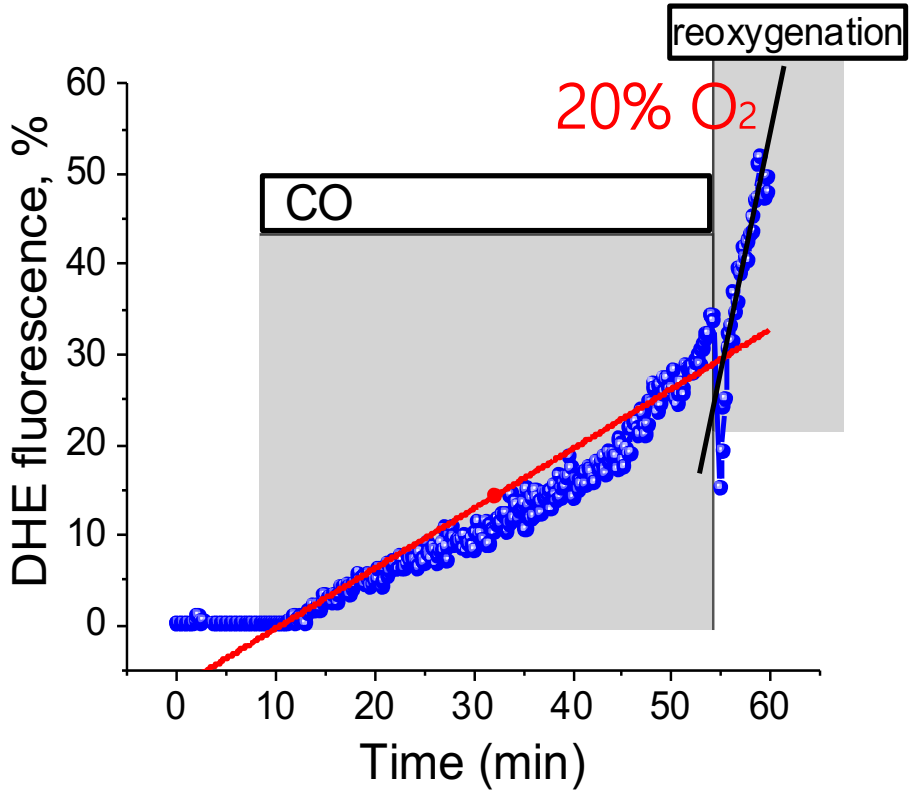
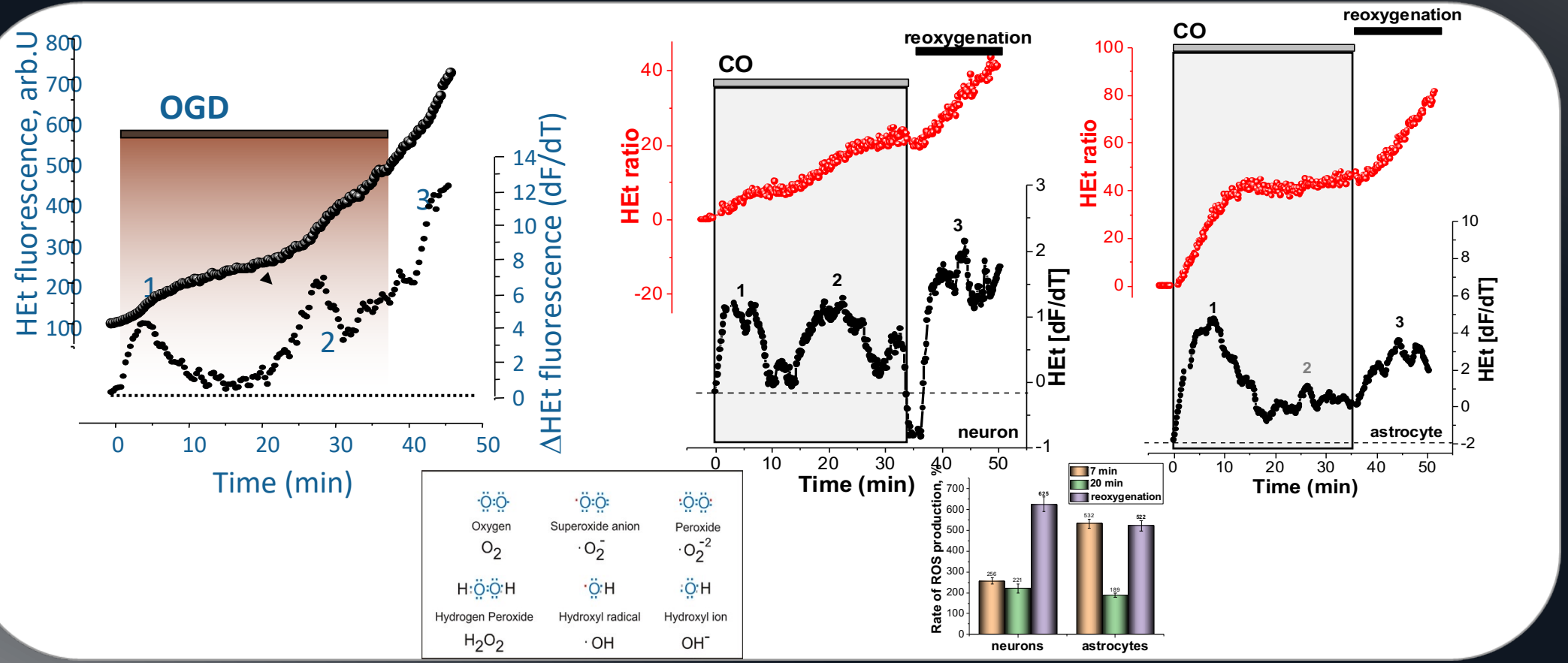
CO triggers ROS production with oxidative burst during reoxygenation



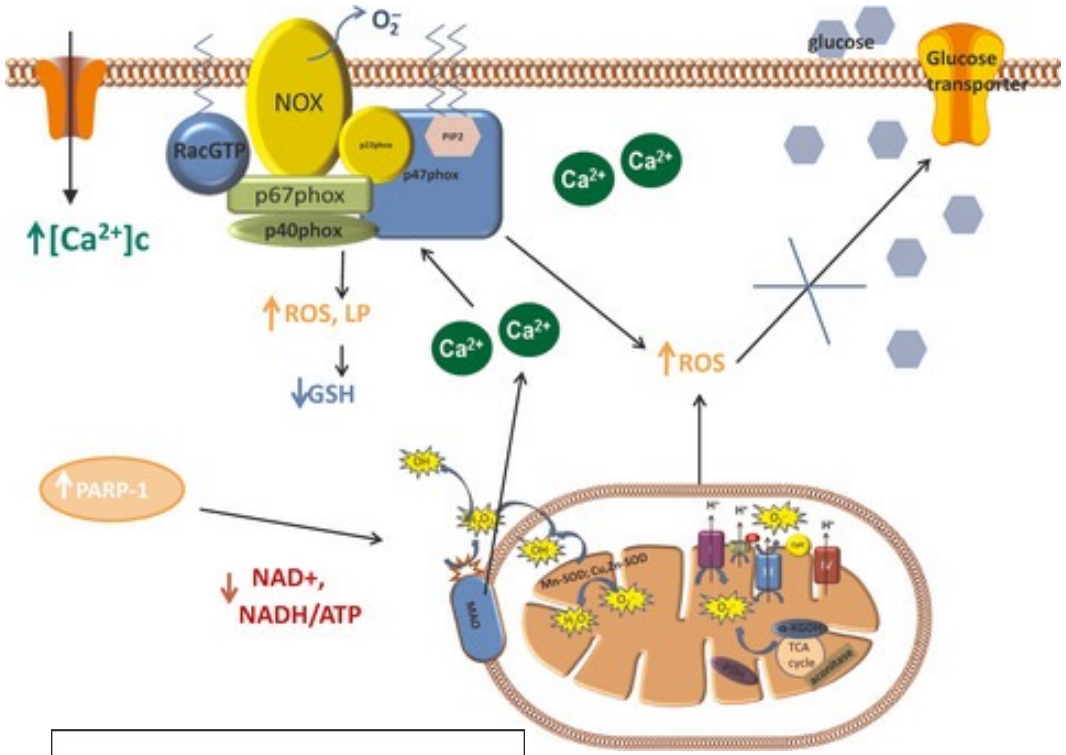


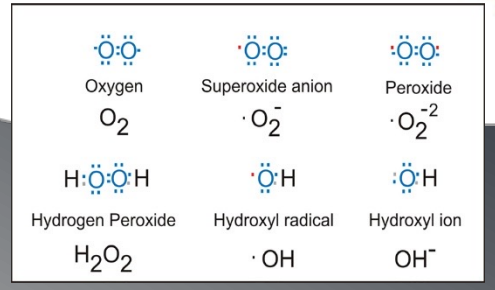
Ischaemia and CO ingestion, both trigger ROS production from different cellular sources

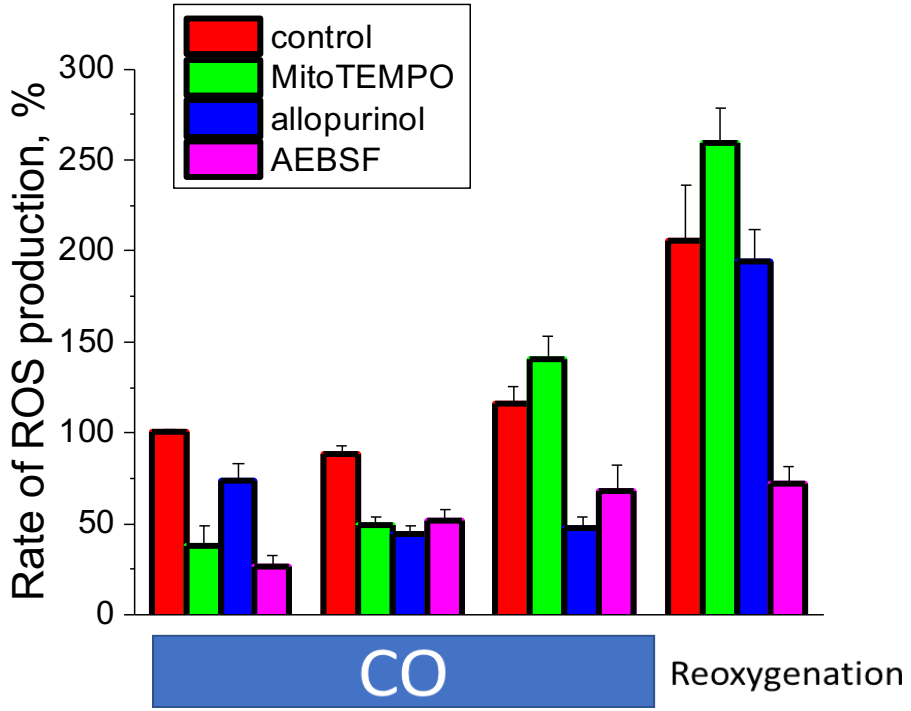


Angelova et al., Redox Biol. 2022

CO-induced ROS production is dependent on various sources







most effective is NOX inhibition

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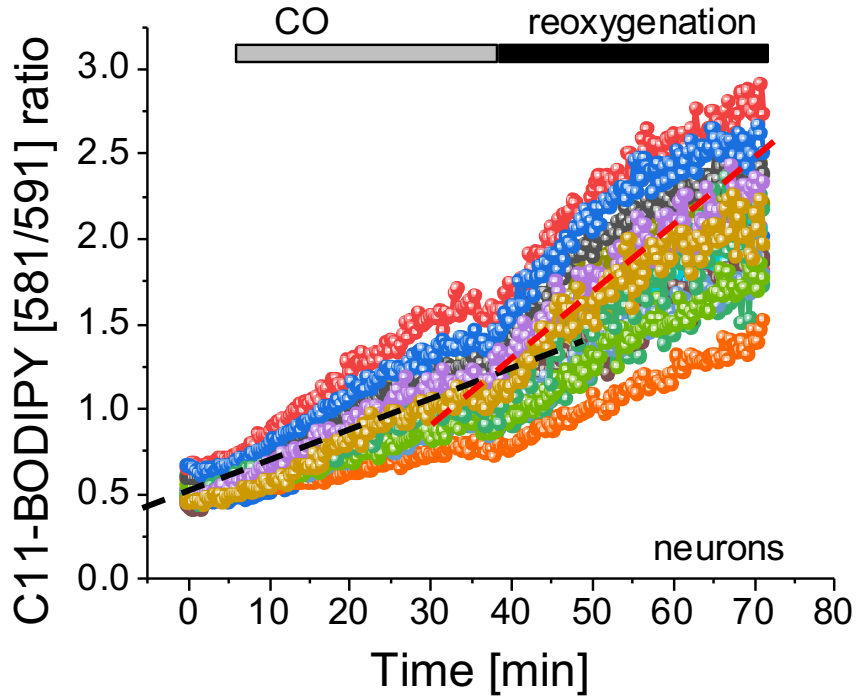
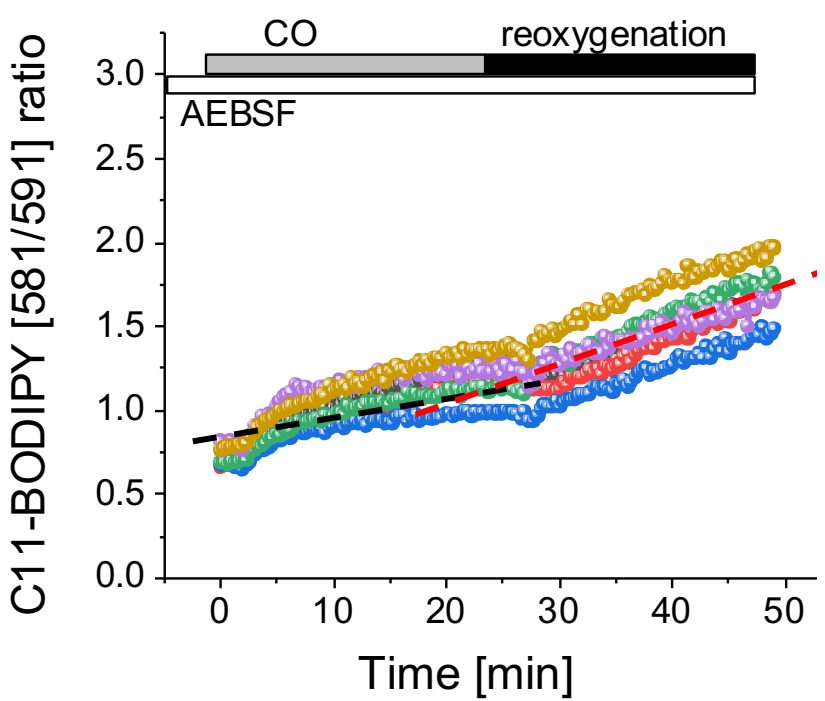
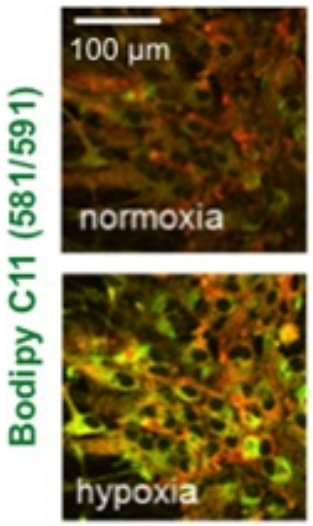
CO-induced oxidative stress is maximal at the time of re-introducing the oxygen







NOX inhibition is most effective at the time of re-oxygenation

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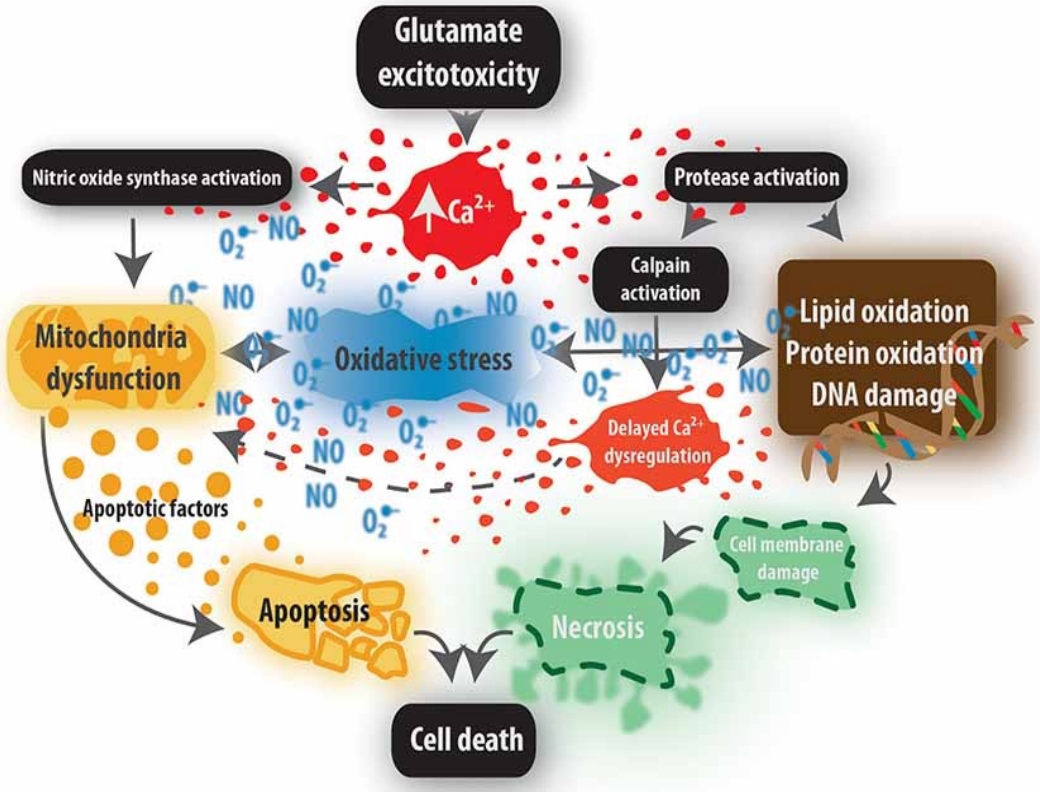
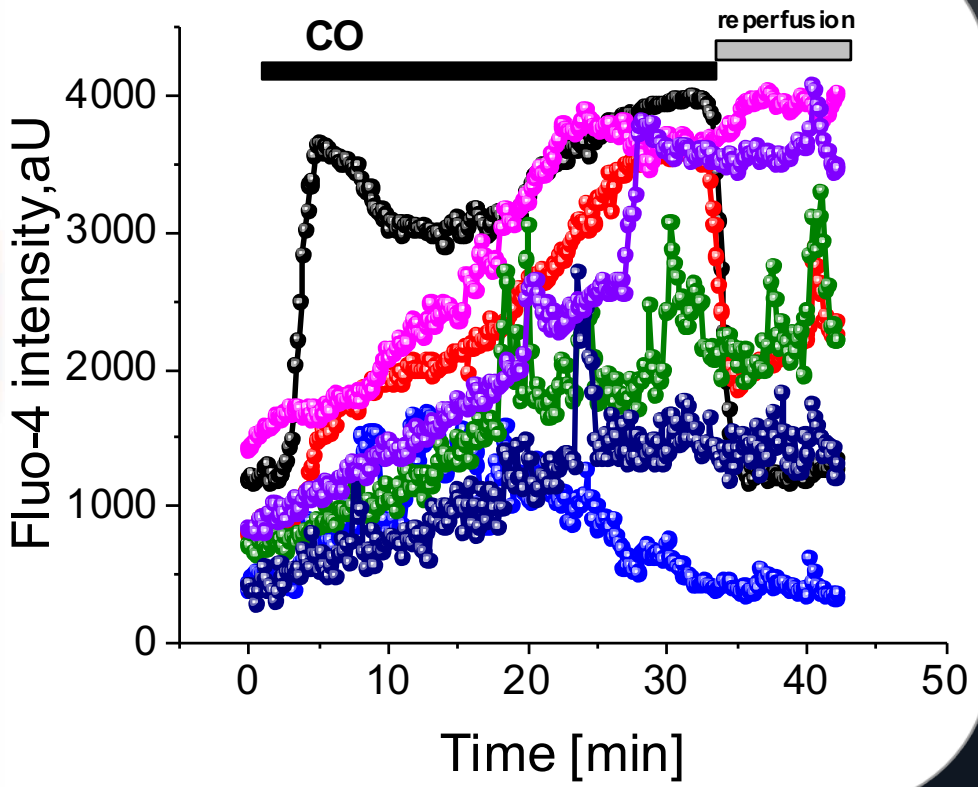
Ischemia-Triggered Glutamate Excitotoxicity in neurons





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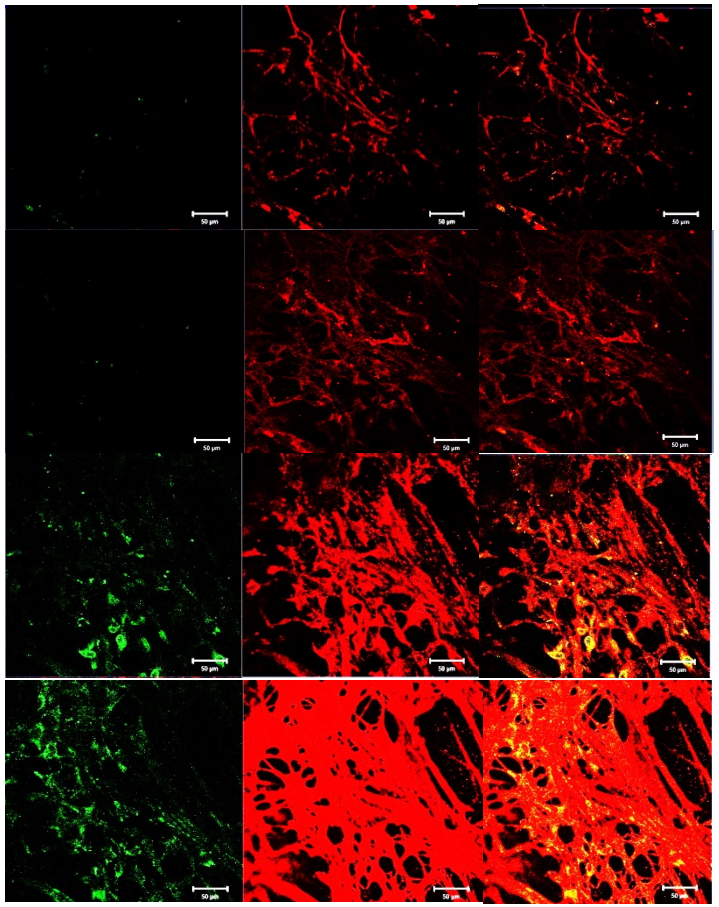
Mitochondrial calcium overload at reoxygenation leads to CO-induced cell death



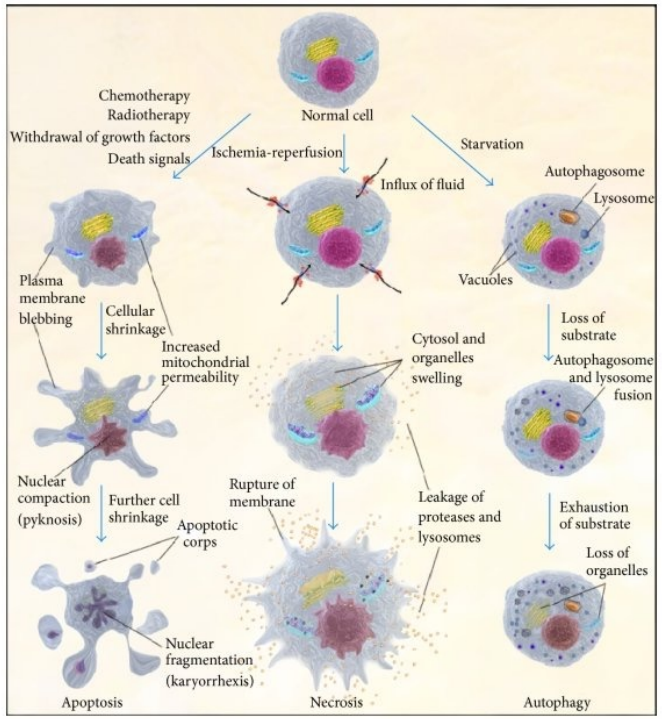
0 min

CO

reperfusion

10 min
after reoxygenation

Caspase-3 substrate-488
Rhod-5N mitochondr ial calcium



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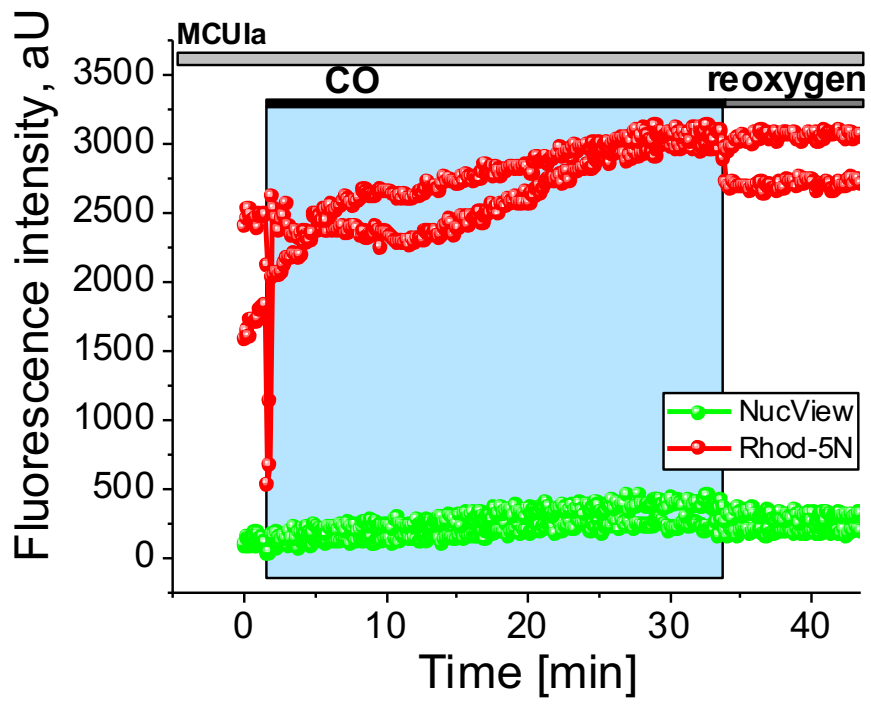
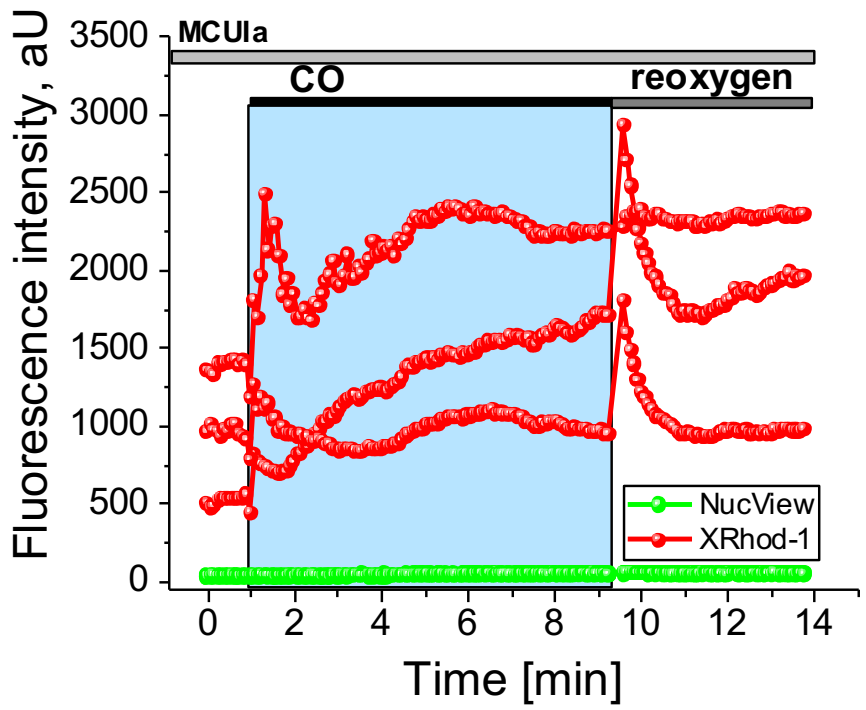
Inhibition of mitochondrial calcium uptake protects neurons against CO-induced cell death at reperfusion





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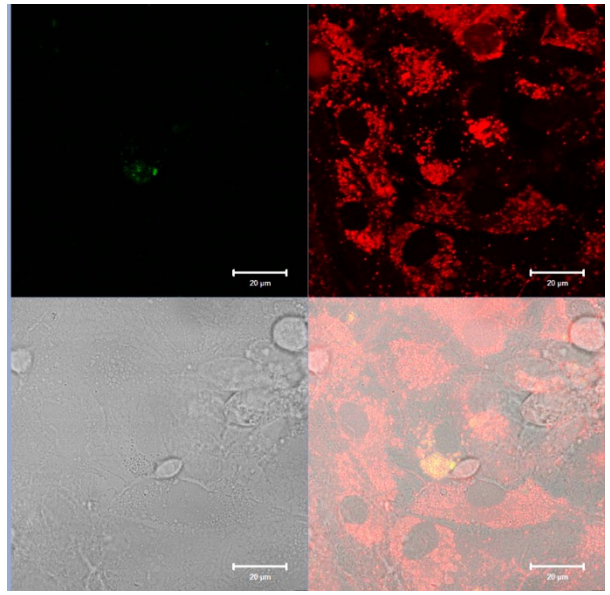
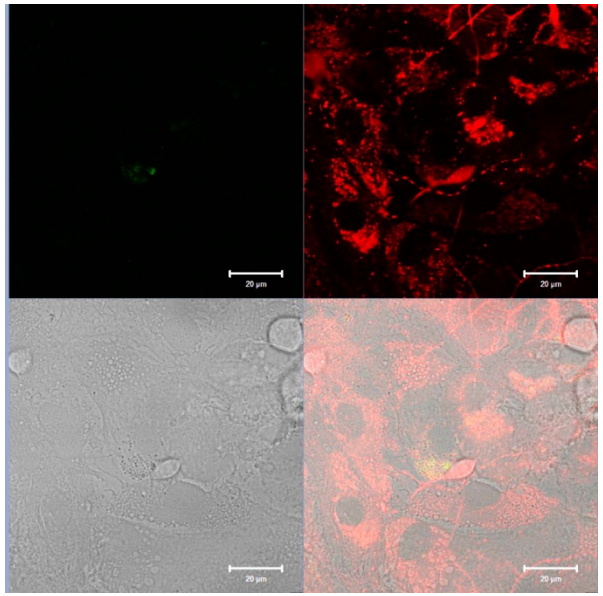
Inhibition of mitochondrial calcium uptake protects neurons against CO-induced cell death at reperfusion

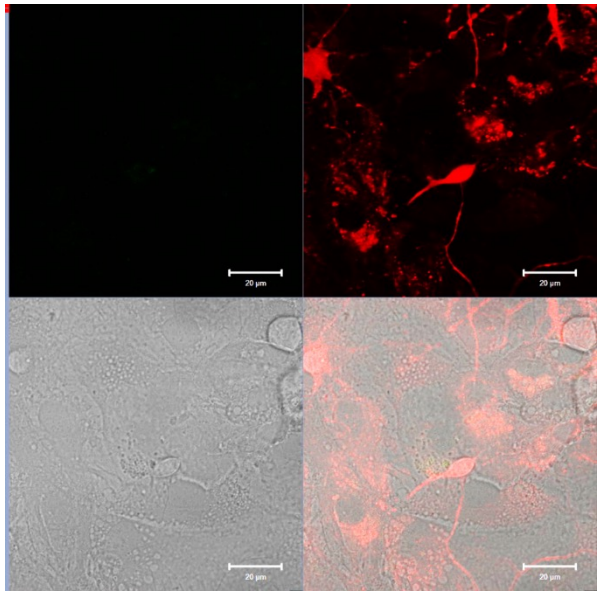
0 min



CO/MCUIa



reoxygenation/MCUIa



Caspase-3 substrate-488
Rhod-5N mitochondrial calcium

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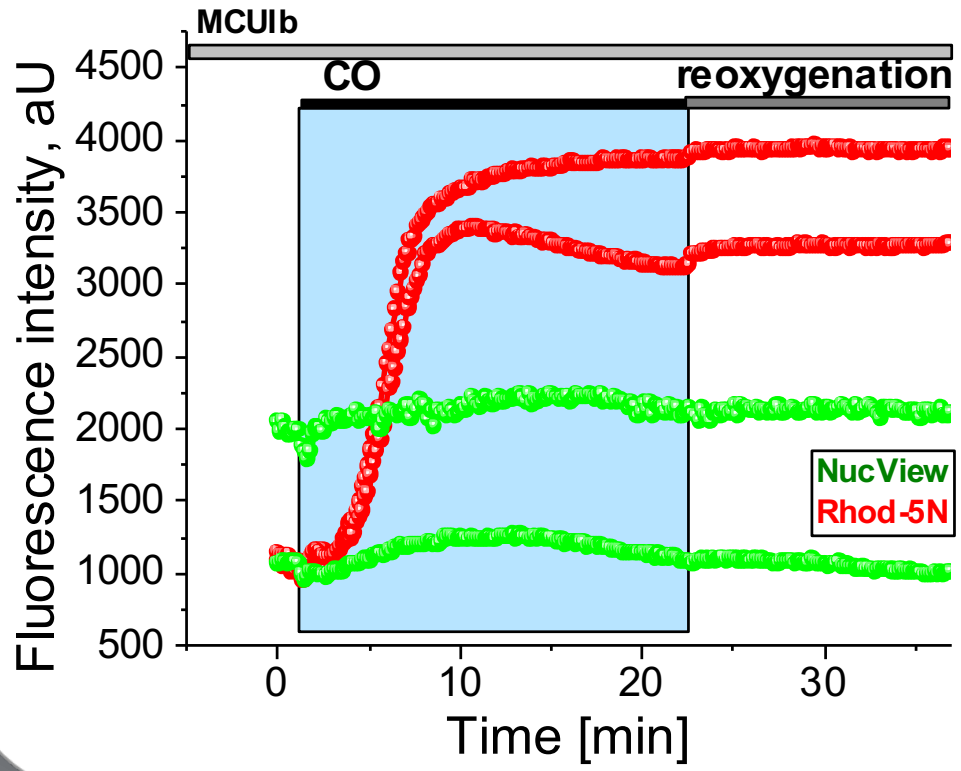

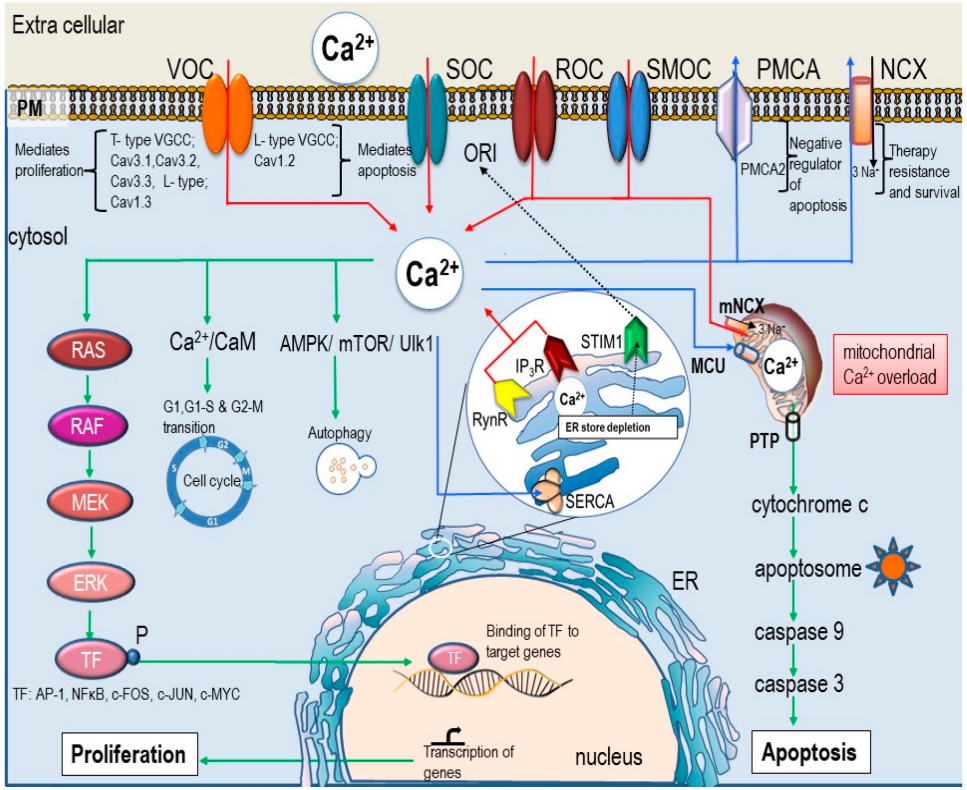

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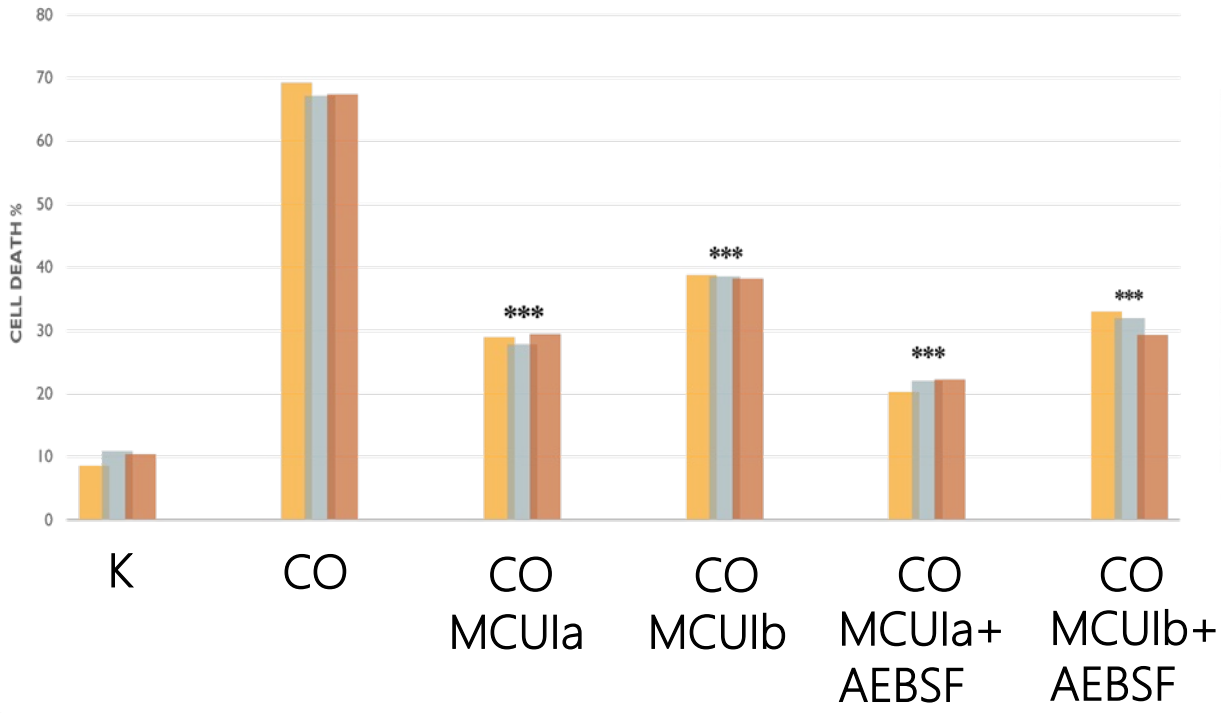
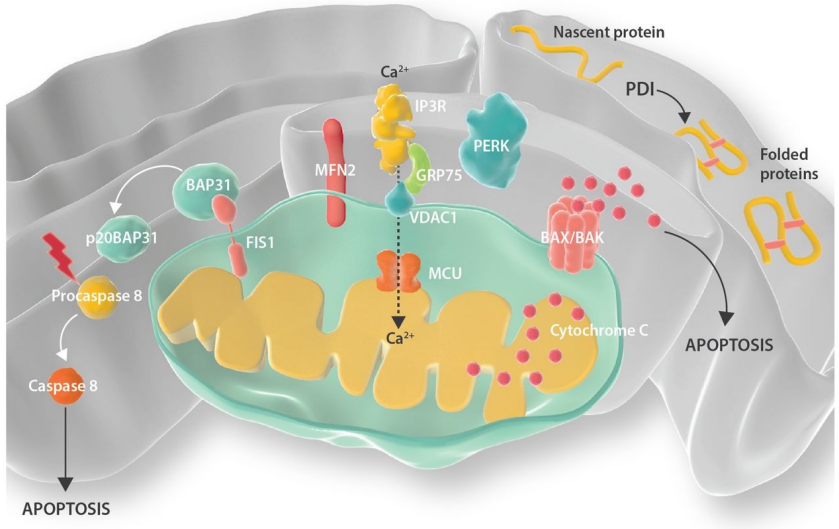
Inhibition of NADPH oxidase and mitochondrial uptake protects neurons against CO-induced cell death





Identification of the most effective compound against reoxygenation-induced neurotoxicity, following CO poisoning

Prof. Andrey Y. Abramov, PhD, DSc

Isabella Myers, BSc DIC MSc MRSB

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