Carbon monoxide as potential cytoprotective factor against ischemic stroke

Encontro Ciência 2020
Ischemic Stroke

1st cause of death in Portugal

2nd cause of death in people above 60 years old

Leading cause of disability

15 million people worldwide suffer ischemic stroke every year

Ischemic stroke Clot impairs the blood flow

- Lack of oxygen and glucose supply
- Reperfusion: oxidative stress

Current therapies limitations:
- Only 30% of patients arrive at hospital at adequate time-period
- Therapies based on re-establishment of blood flow
**Strategy:** Window for therapeutic opportunities – Penumbra theory

**Penumbra**
- Apoptosis
- Inflammation
- Autophagy

**Hours/days**

Core of lesion - Necrosis  *minutes*

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**Molecular and Cellular Mechanisms following Stroke**

**Lesion**
- Necrosis
- Excitotoxicity
- Apoptosis
- Autophagy
- Inflammation

**Protection**
- Anti-excitotoxicity
- Anti-inflammation
- Anti-apoptosis
- Regeneration & repair

**New drugs / strategies**

**Target!**
1949 - CO was found to be an endogenous molecule, exhaled by healthy humans (Sjostrand 1949)
1968 – Heme oxygenase was described as the enzyme that degrades heme producing CO (Tenhunen 1968)
1993 – described CO as neuromodulator (Verma 1993)
Last 20 years - boom of CO’s Biology research
✓ Carbon monoxide is an endogenous molecule
✓ HO: Heme-oxygenase – stress enzyme

Carbon Monoxide (CO)

CARBON MONOXIDE (CO) POISONING
CAN’T BE SEEN  CAN’T BE SMELLED  CAN’T BE HEARD  CAN BE STOPPED

Haem group
Released from dying erythrocytes in the spleen

Haem-oxygenase (HO)

HO-1 (inducible)
HO-2 (constitutive)

Fe²⁺ + Biliverdin → Bilirubin

Biliverdin reductase

CO
Carbon monoxide

**Main beneficial biological functions**

- Anti-apoptotic/Cytoprotection
- Anti-proliferative
- Anti-inflammatory
- Preconditioning
- Cardioprotective
- Metabolism modulation
- Modulation of cell differentiation

ROS are key signaling molecules in CO’s mode of action

For review:
- Motterlini & Otterbein (2010) *Nat Rev Drug Discov*
- Queiroga & Vieira (2015) *British J Pharmacol*
- Figueiredo-Pereira & Vieira (2020) *Redox Biol*
Neural cells

Biological processes:
- Cell Death
- Cell Metabolism
- Neuroinflammation
- Autophagy
Summary of research on CO Biology developed in our lab:

**CO’s anti-apoptotic role in**
- Neurons: Vieira et al. 2008 J Neurochem
- Queiroga et al. 2012 PlosONE
- Queiroga et al. 2016 J Cell Sci

**CO’s inflammatory role in**
- Astrocytes: Queiroga et al. 2010 J Biol Chem
- Almeida et al. 2012 J Biol Chem
- Oliveira et al. 2018 Mol Neurobiol
- Figueiredo-Pereira et al. 2019 FEMS Yeast Res

**CO’s anti-apoptotic role in**
Summary of research on CO Biology developed in our lab:

**CO’s stimulation of neuronal differentiation**

Almeida et al. *PlosONE* 2016  
Dreyer-Andersen et al. *PlosONE* 2018  
Almeida et al. *Redox Biol* 2018
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