Mitochondria, melatonin, and neuroinflammation in Parkinson's disease

Darío Acuña Castroviejo
Biomedical Research Center
Health Sciences Technology Park
University of Granada, Spain

dacuna@ugr.es
- Retina
- Immune cells
- Intestinal epithelium
- Ovary
- Testicles
- Liver
- Brain
- Heart
- Placenta
- Bone marrow
- Cerebrospinal fluid
- Bile
- AANAT and ASMT expressed in all tissues

Suofu Y et al. PNAS 2017; suppl/doi:10.1073/pnas.1705768114

Circadian clock

Autophagy
Metabolism
Antioxidant defence
DNA repair
Melatonin

Oxidation of proteins, lipids and organelles

Intracellular and extracellular aggregates

Oxidative stress

Oxidation of DNA

Neurodegeneration

Brain cell death

Circadian network

DBP–E4BP4 loop
PER–CRY loop
ROR–REV–ERB loop

CRY
PGC1α
RO1s
BMAL1

G6P

NAD+ biosynthesis

Sirtuin

Supporting life

Metabolic network

Gluconeogenesis
Glycolysis

Glucose

Amino acids

Pyruvate

Acetyl-CoA

TCA cycle

Fatty acids

Lipids

Electron transport and oxidative phosphorylation

NADH

AMP
ADP
ATP
Pi

Nature Reviews Neuroscience 2012; 13, 325-335

Clocks not winding down: unravelling circadian networks

Neuroinflammation: iNOS
Excitotoxicity: nNOS
Oxidative stress

MAIN QUESTIONS:

iNOS/nNOS participate in the mitochondrial impairment during PD?

Could melatonin counteract the respiratory failure in PD?

López A et al. Plos One 2017; doi.org/10.1371/journal.pone.0183090
STUDIES ON iNOS- and nNOS-DEFICIENT MICE

López A et al. Plos One 2017; doi.org/10.1371/journal.pone.0183090
Mitochondrial oxygen consumption decreased sharply after MPTP administration in SN and ST of all strains, independently of the presence or absence of iNOS/nNOS. The effect of MPTP was prevented by melatonin treatment. The effects are mainly observed in CI+CII.

López A et al. Plos One 2017; doi.org/10.1371/journal.pone.0183090
Therefore, neuroinflammation and mitochondrial dysregulation seem to act in parallel in the MPTP model of PD.

Melatonin counteract the effects of MPTP, restoring mitochondria and reducing neuroinflammation

López A et al. Plos One 2017; doi.org/10.1371/journal.pone.0183090
MAIN QUESTIONS:

Mitochondrial respiration *in vivo* behaves as in isolated mitochondria? Could melatonin counteract the respiratory failure in PD? Could melatonin recover from mitochondria failure?
aMT PREVENTS MITOCHONDRIAL BIOENERGETIC DISFUNCTION

Diaz-Casado E et al. Zebrafish 2018; doi:10.1089/zeb.2017.1479
**A** Basal respiration OCR (pmol/min/mg protein) with MPTP and aMT.

**B** ETS capacity OCR (pmol/min/mg protein) with MPTP and aMT.

**C** Protein leak (%) with MPTP and aMT.

**D** LE ratio with MPTP and aMT.

**E** ATP turnover (%) with MPTP and aMT.

**F** OCR (pmoles/min) with MPTP and aMT treatments.

**RECOVERS MIOTOCNDRIAL BIOENERGETIC FUNCTION**

Diaz-Casado E et al. Zebrafish 2018; doi:10.1089/zeb.2017.1479
aMT RECOVERS MOTOR PERFORMANCE

(A) Total distance (cm) vs. Control, MPTP, +aMT 5 days, +aMT 2 days

(B) Speed (cm/s) vs. Control, MPTP, +aMT 5 days, +aMT 2 days

(C) arena activity plots for Control, MPTP, +aMT 5 days, +aMT 2 days

Diaz-Casado E et al. Zebrafish 2018; doi:10.1089/zeb.2017.1479
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