Mitochondria, melatonin, and neuroinflammation in Parkinson's disease

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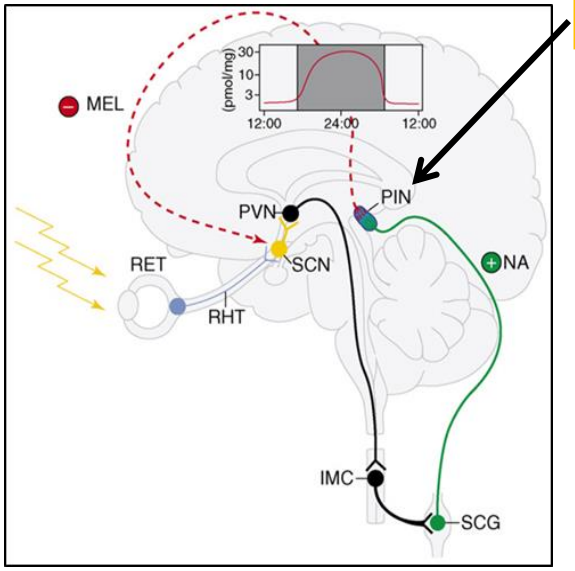
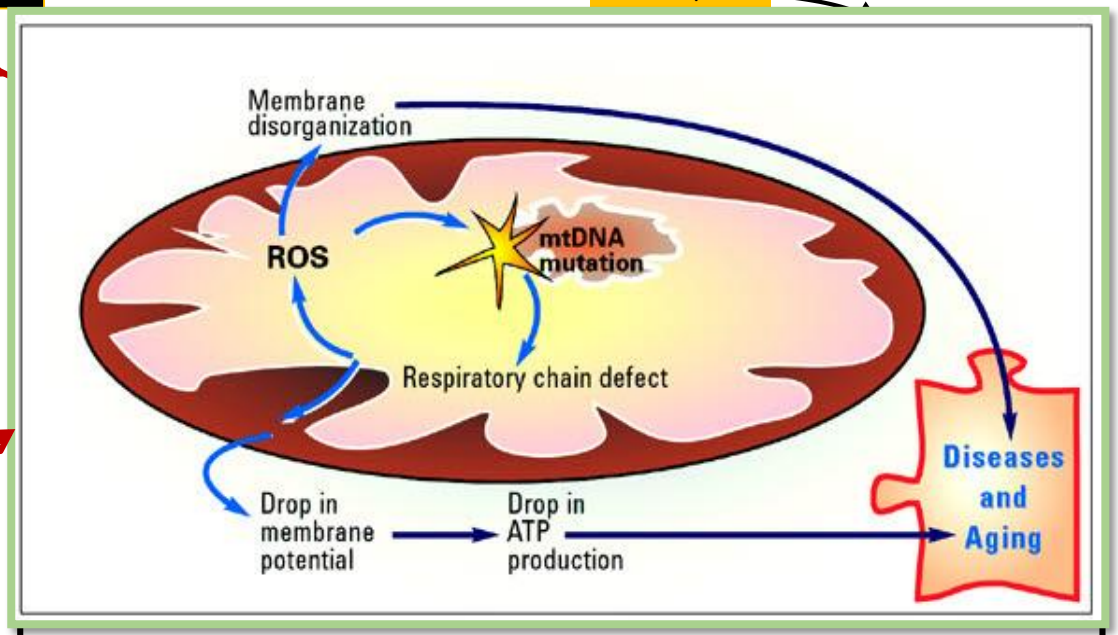
13th Conference on Mitochondrial Physiology
The role of mitochondria in health, disease and drug discovery
COST MitoEAGLE perspectives and MitoEAGLE WG and MC Meeting

MiP2018/MitoEAGLE, Jurmala, Latvia, 18 – 21 Sep 2018



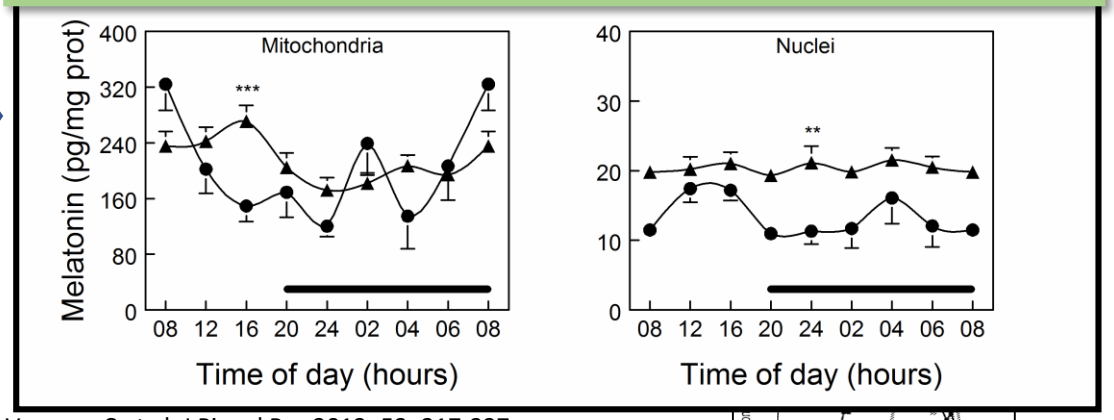
PINEAL: 0.5 nM

BLOOD/CSF



EXTRAPINEAL: 1-10 µM

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



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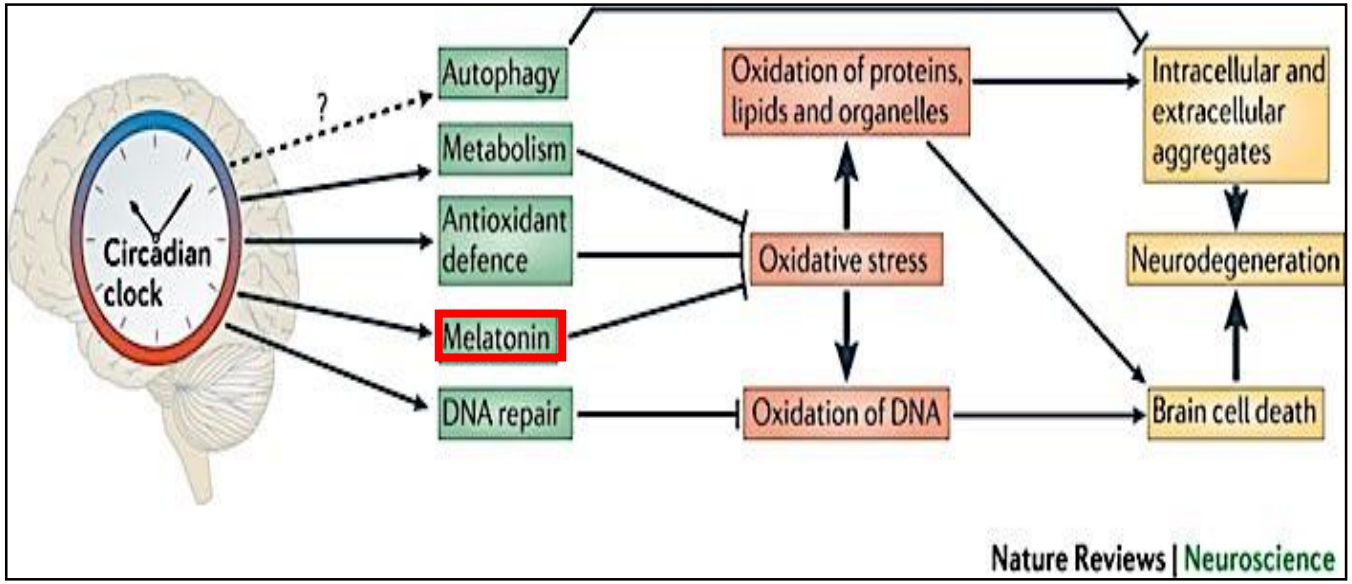

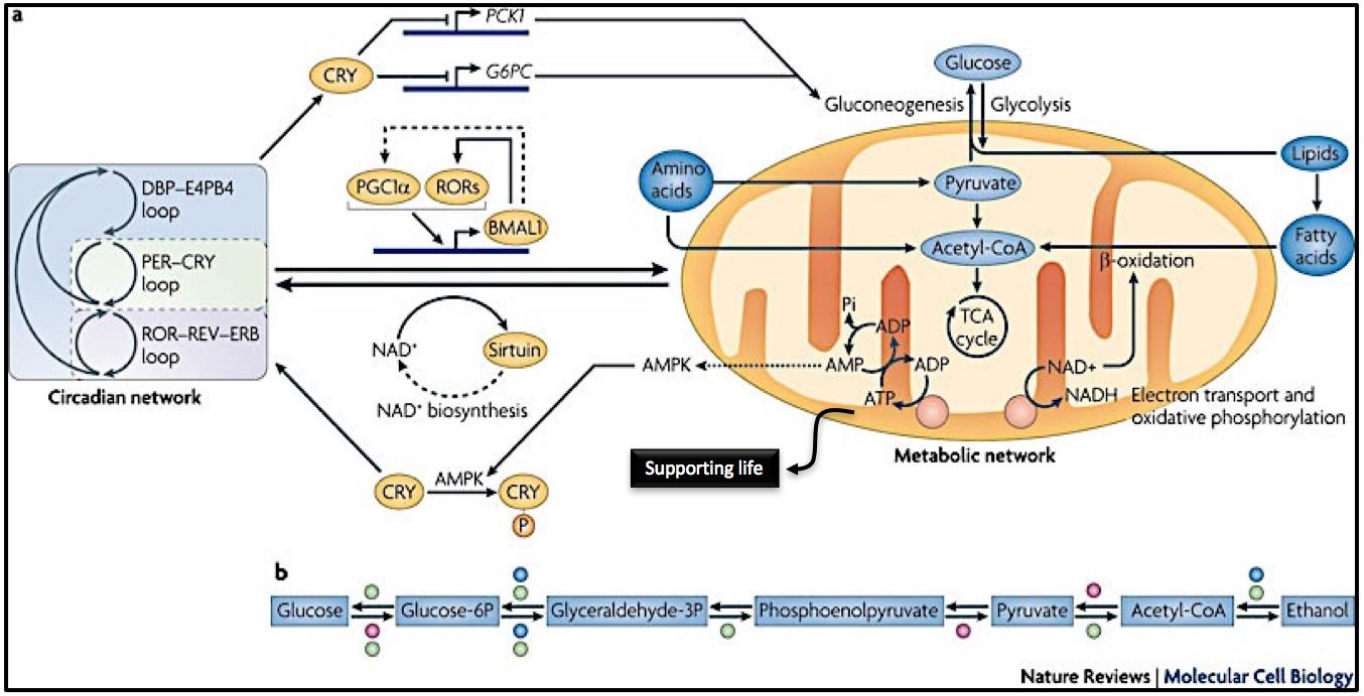

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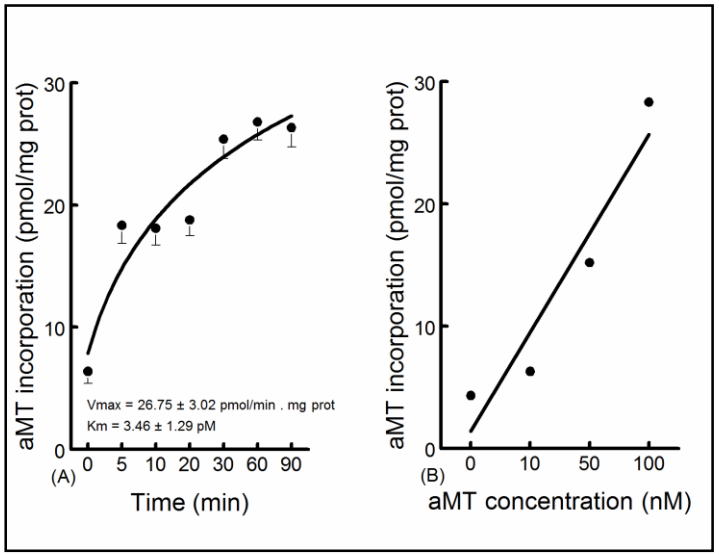
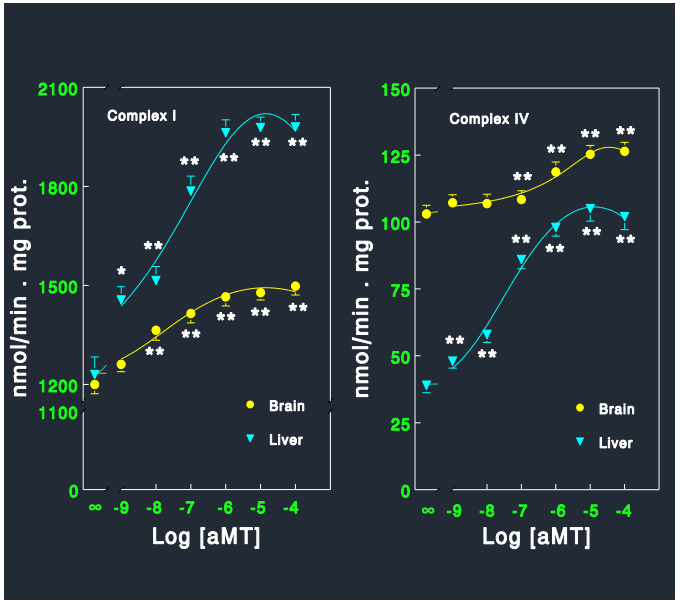
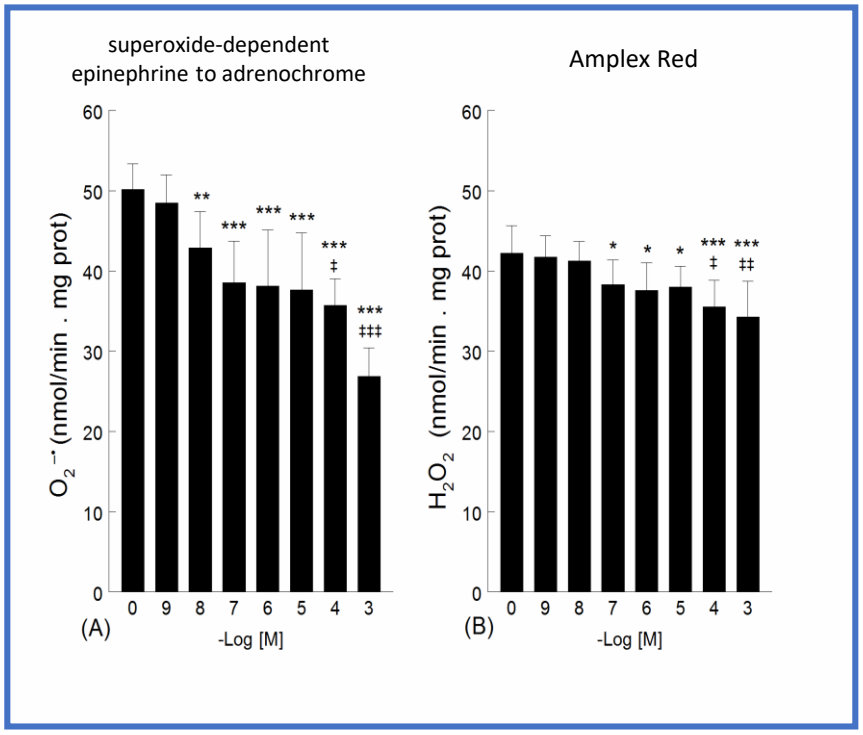
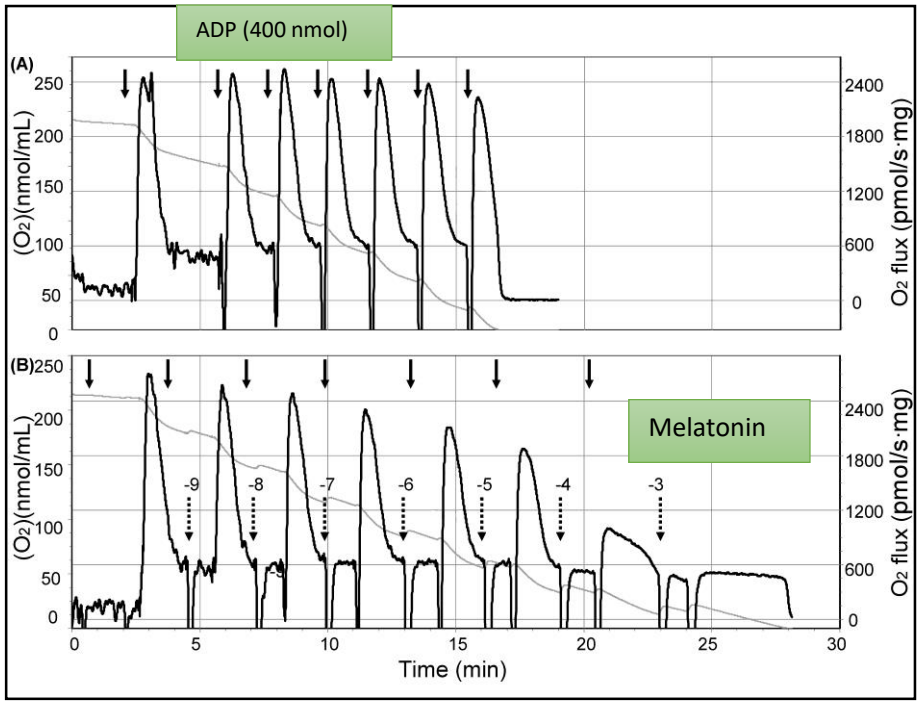
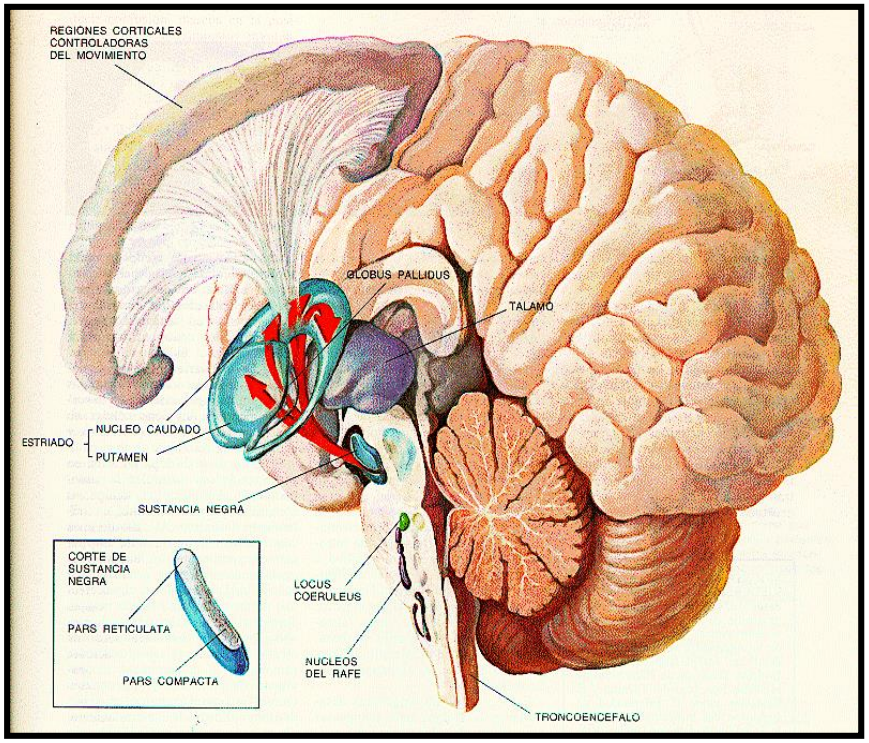








López A et al. J Pineal Res 2009; 46:188-198



Neuroinflammation: iNOS
Excitotoxicity: nNOS
Oxidative stress

?

Mitochondrial failure: CI

CELL DEATH

THasa Reduction
Loss OF DA

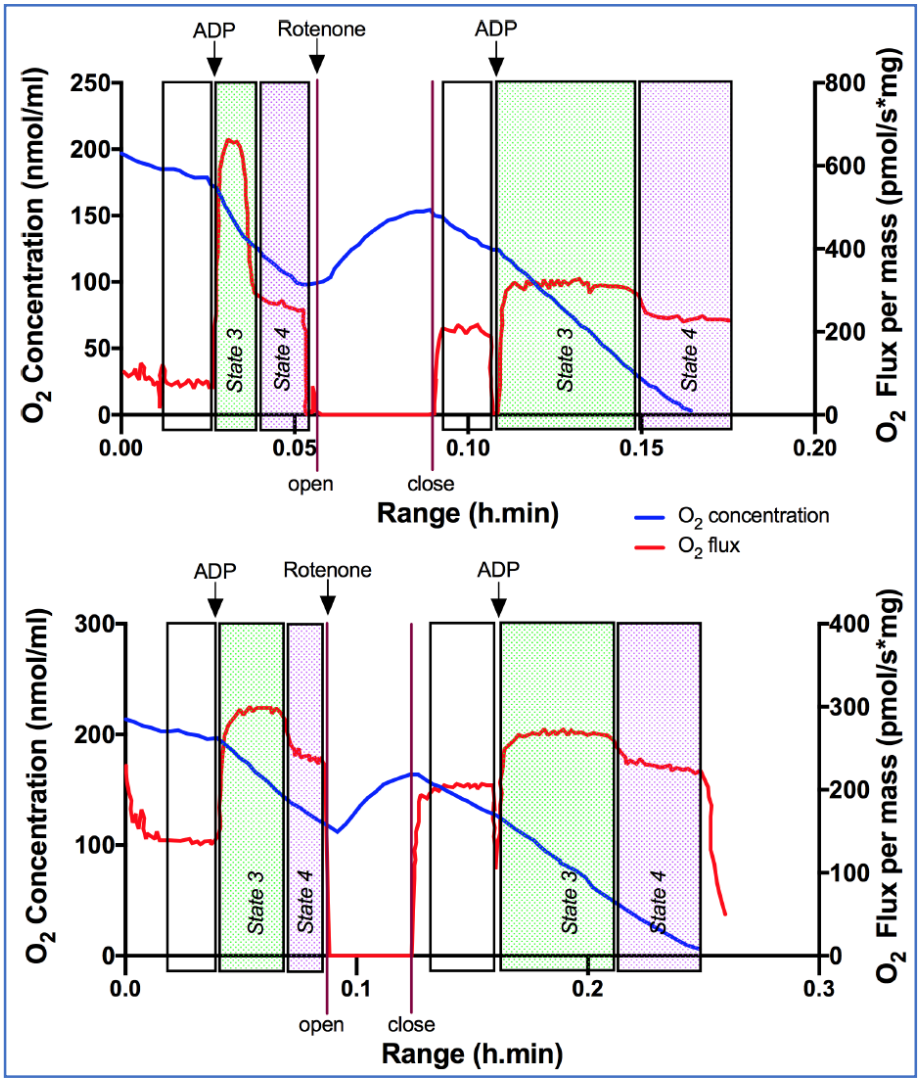
MAIN QUESTIONS:

iNOS/nNOS participate in the mitochondrial impairment during PD?

Could melatonin counteract the respiratory failure in PD?

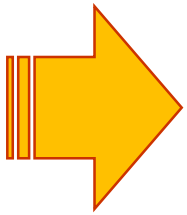
López A et al. Plos One 2017; doi.org/10.1371/journal.pone.0183090

STUDIES ON iNOS- and nNOS-DEFICIENT MICE



SN + Vehicle

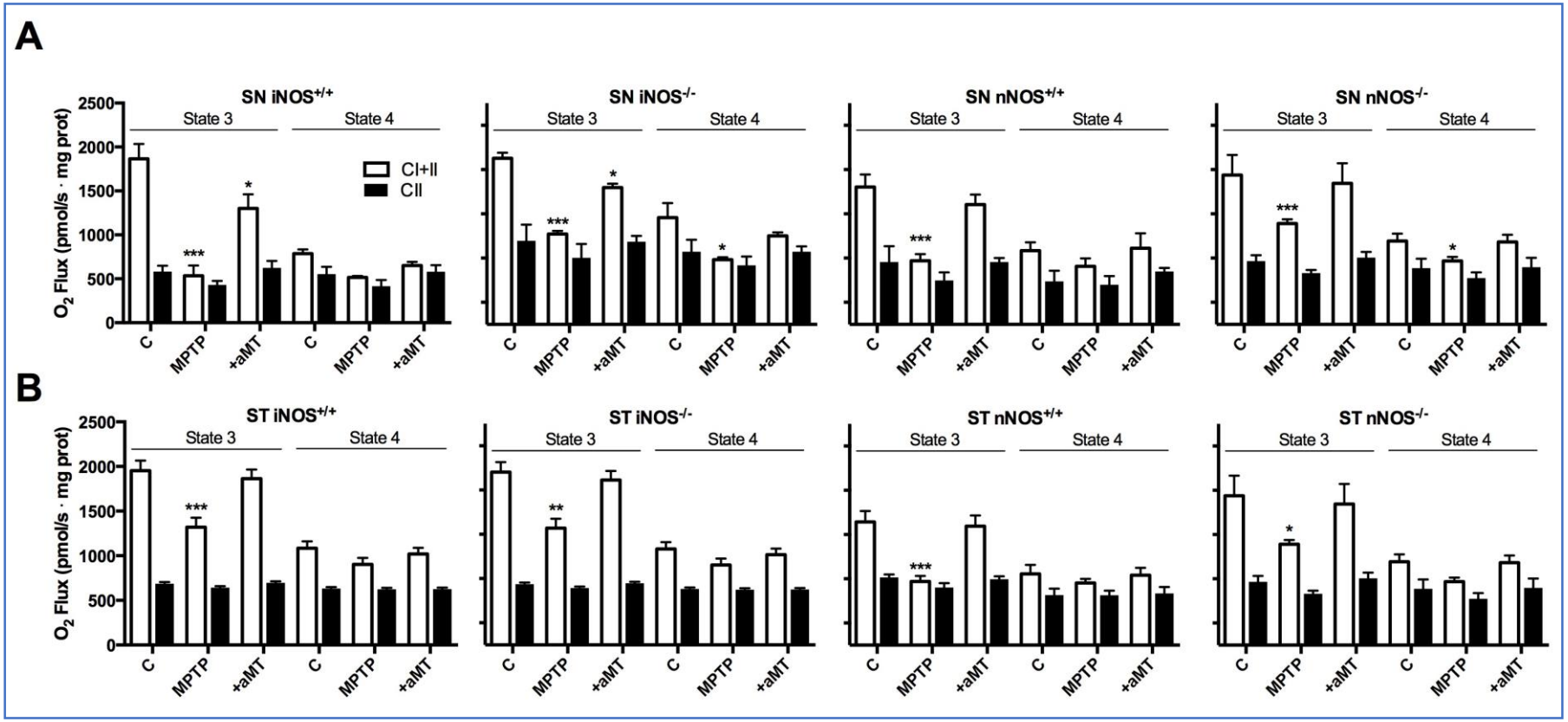
SN + MPTP



↑ROS
↓RCR
↓ADP:O
↓ATP

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

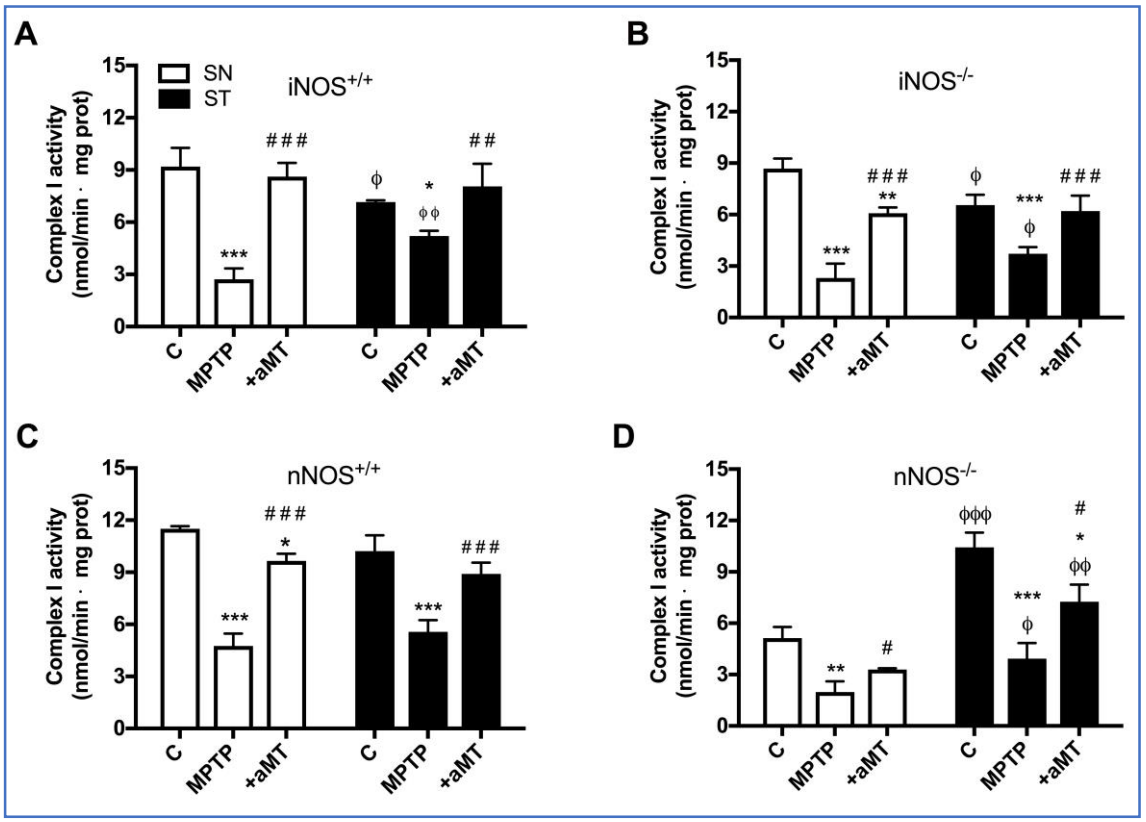
iNOS$^{+/+}$ iNOS$^{-/-}$ nNOS$^{+/+}$ nNOS$^{-/-}$

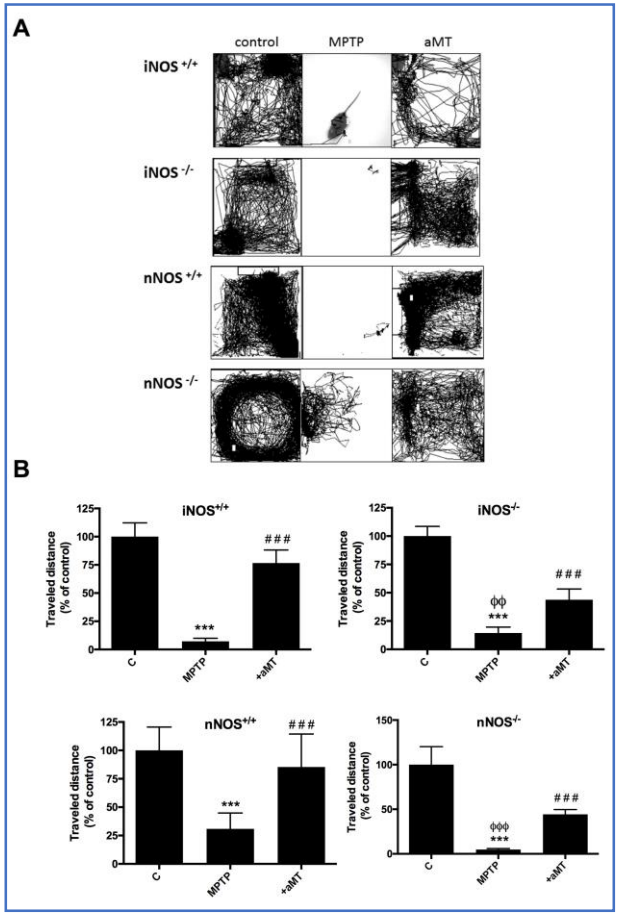


Mitochondrial oxygen consumption **decreased sharply after MPTP** administration in SN and ST of all strains, **independently of the presence or absence of iNOS/nNOS**. The effect of MPTP was **prevented by melatonin treatment**.

The effects are mainly observed in **CI+CII**.

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

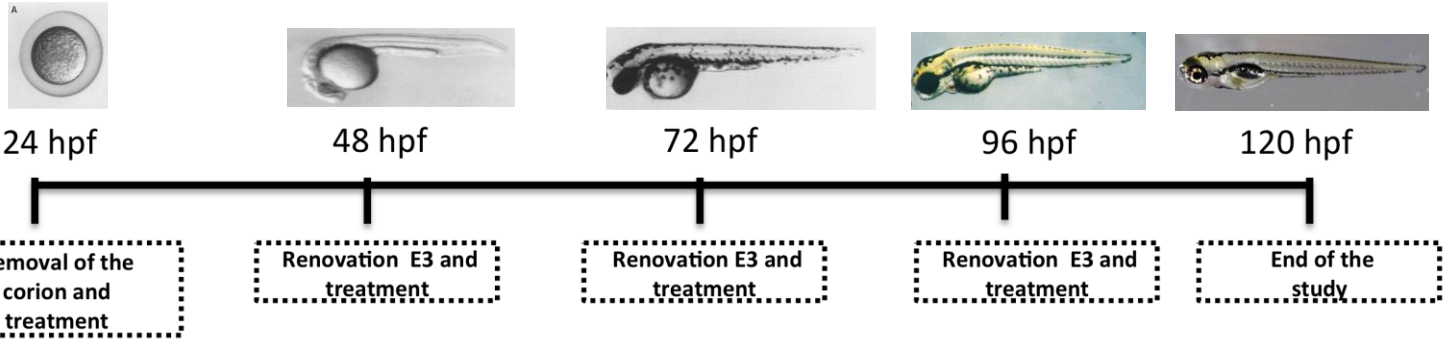


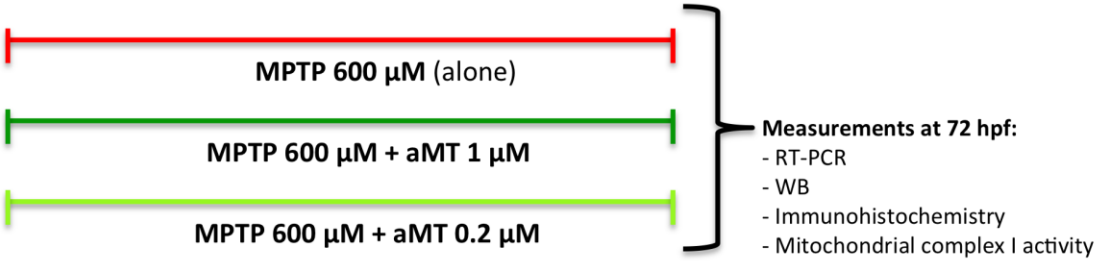


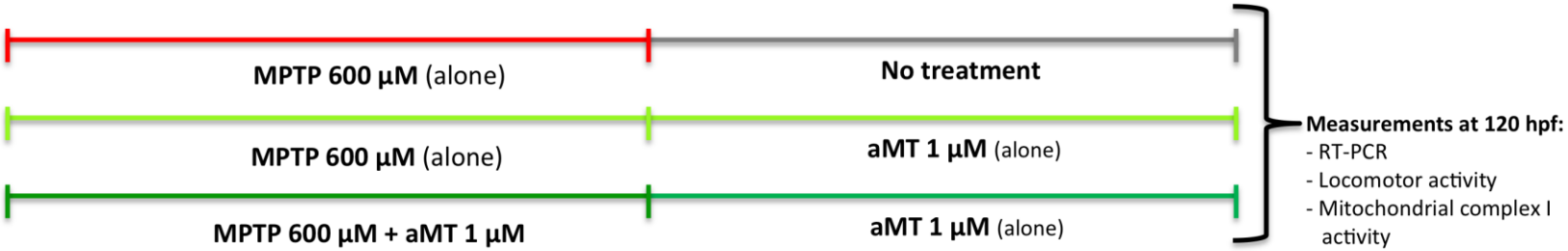
Therefore, neuroinflammation and mitochondrial dysregulation **seem to act in parallel in the MPTP model of PD**.

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



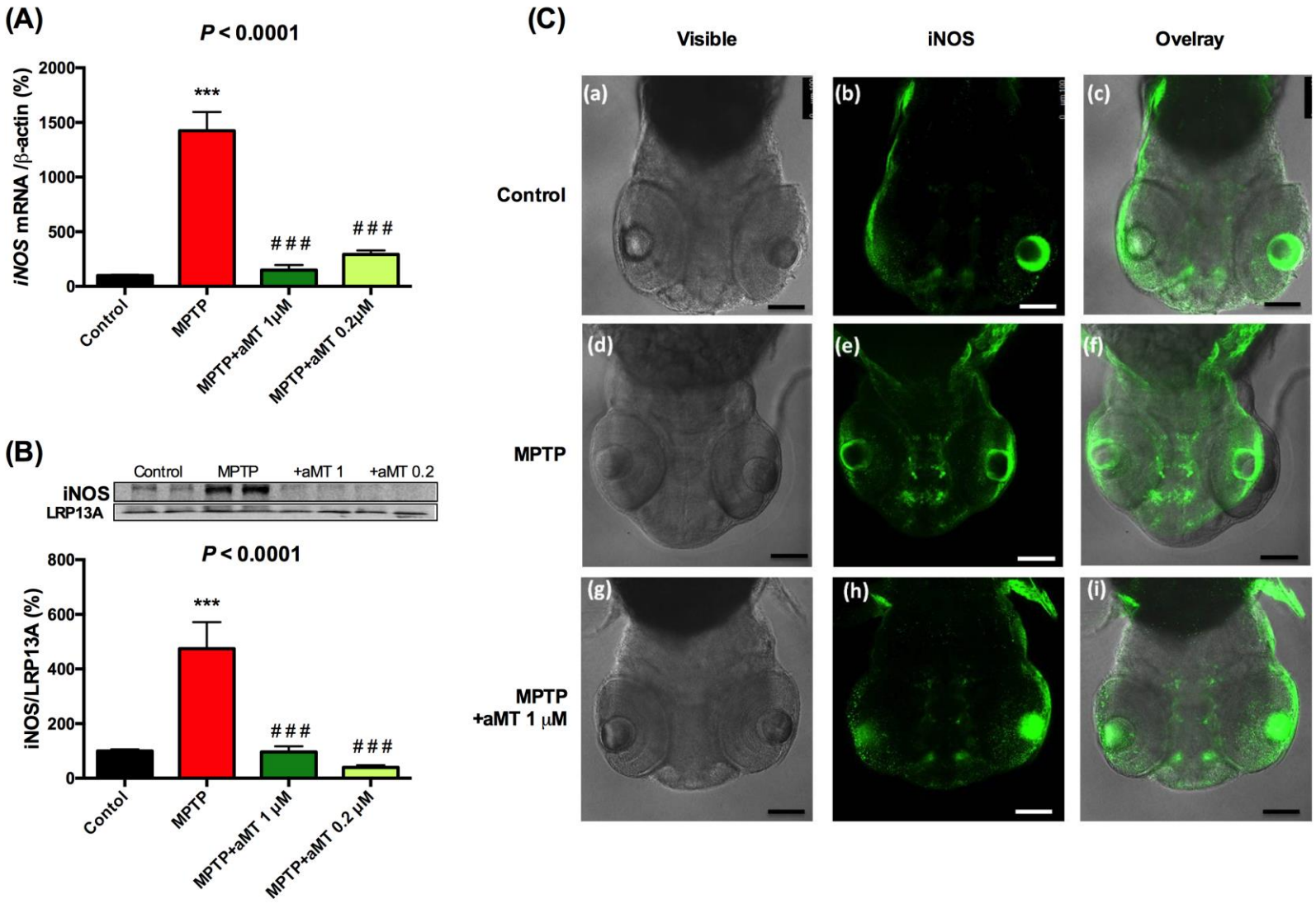


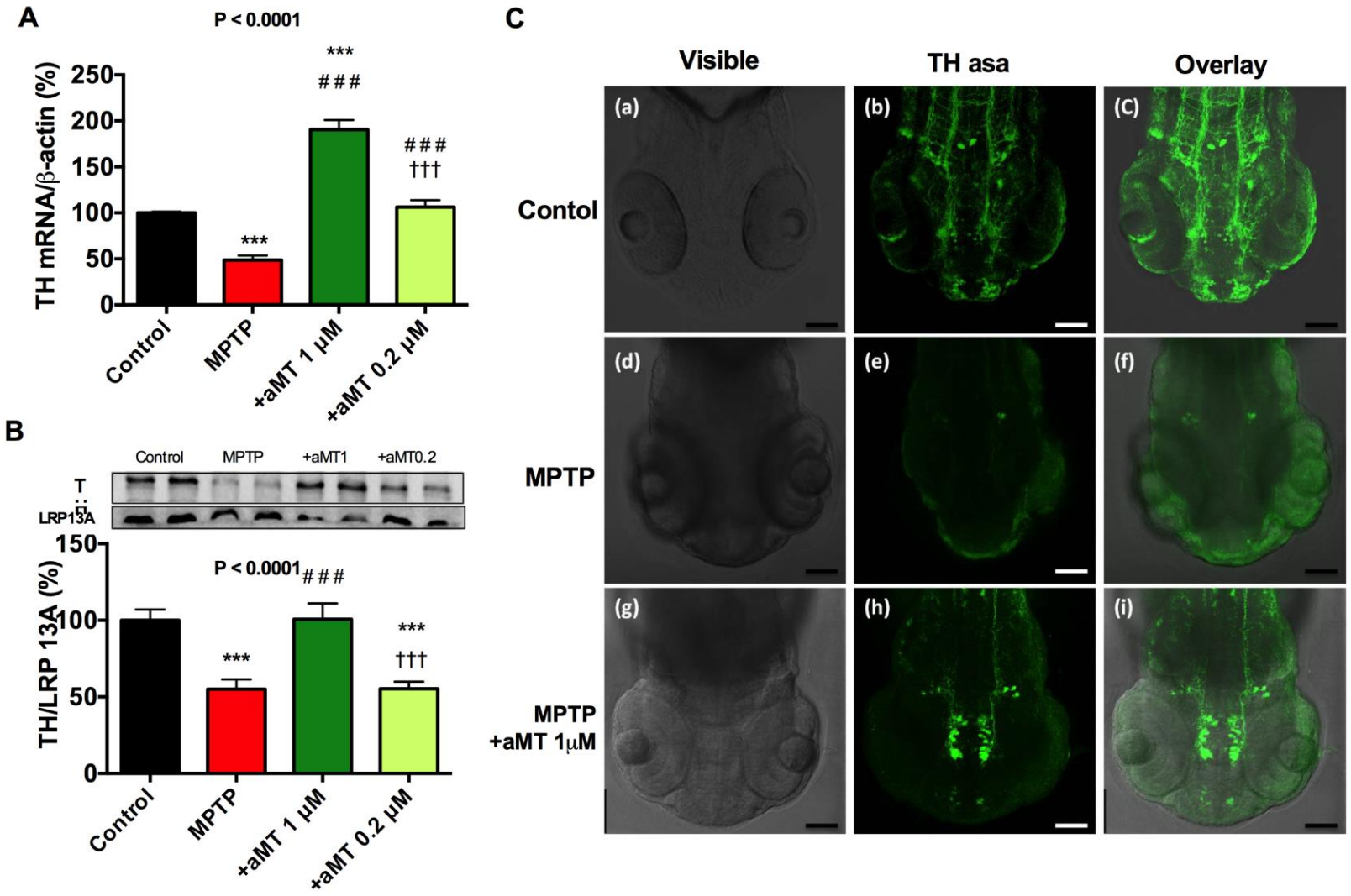


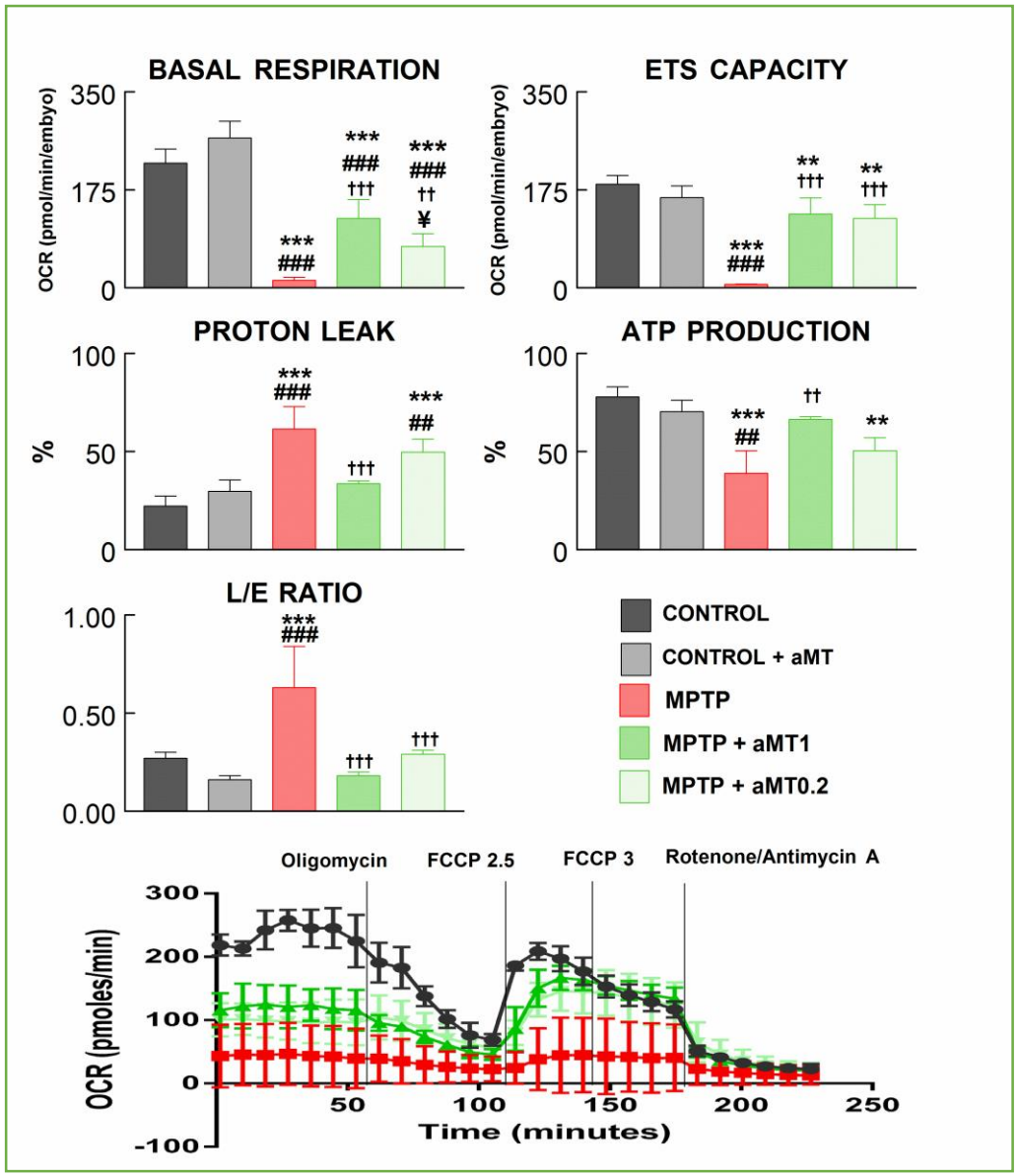
MAIN QUESTIONS:

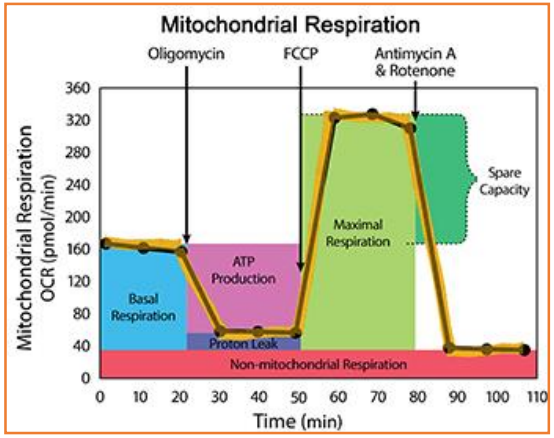
Mitochondrial respiration *in vivo* behaves as in isolated mitochondria?
Could melatonin counteract the respiratory failure in PD?
Could melatonin recover from mitochondria failure?

Diaz-Casado E et al. J Pineal Res 2016; doi:10.1111/jpi.12332
Diaz-Casado E et al. Zebrafish 2018; doi:10.1089/zeb.2017.1479


(A)
P < 0.0001
iNOS mRNA /β-actin (%)
2000
1500
1000
500
0
***
###
###
Control
MPTP
MPTP+aMT 1μM
MPTP+aMT 0.2μM
(B)
Control
MPTP
+aMT 1
+aMT 0.2
iNOS
LRP13A
P < 0.0001
iNOS/LRP13A (%)
800
600
400
200
0
***
###
###
Contol
MPTP
MPTP+aMT 1 μM
MPTP+aMT 0.2 μM
(C)
Visible
iNOS
Ovelray
Control
MPTP
MPTP
+aMT 1 μM
(a)
(b)
(c)
(d)
(e)
(f)
(g)
(h)
(i)


A
P < 0.0001
TH mRNA/β-actin (%)
250
200
150
100
50
0
***
###
***
###
†††
Control
MPTP
+aMT 1 µM
+aMT 0.2 µM
B
Control
MPTP
+aMT1
+aMT0.2
T
LRP13A
TH/LRP 13A (%)
150
100
50
0
P < 0.0001
###
***
***
†††
Control
MPTP
+aMT 1 µM
+aMT 0.2 µM
C
Visible
TH asa
Overlay
Contol
MPTP
MPTP
+aMT 1µM
(a)
(b)
(C)
(d)
(e)
(f)
(g)
(h)
(i)





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PREVENTS MIOTOCHONDRIAL BIOENERGETIC DISFUNCTION

Diaz-Casado E et al. J Pineal Res 2016; doi:10.1111/jpi.12332
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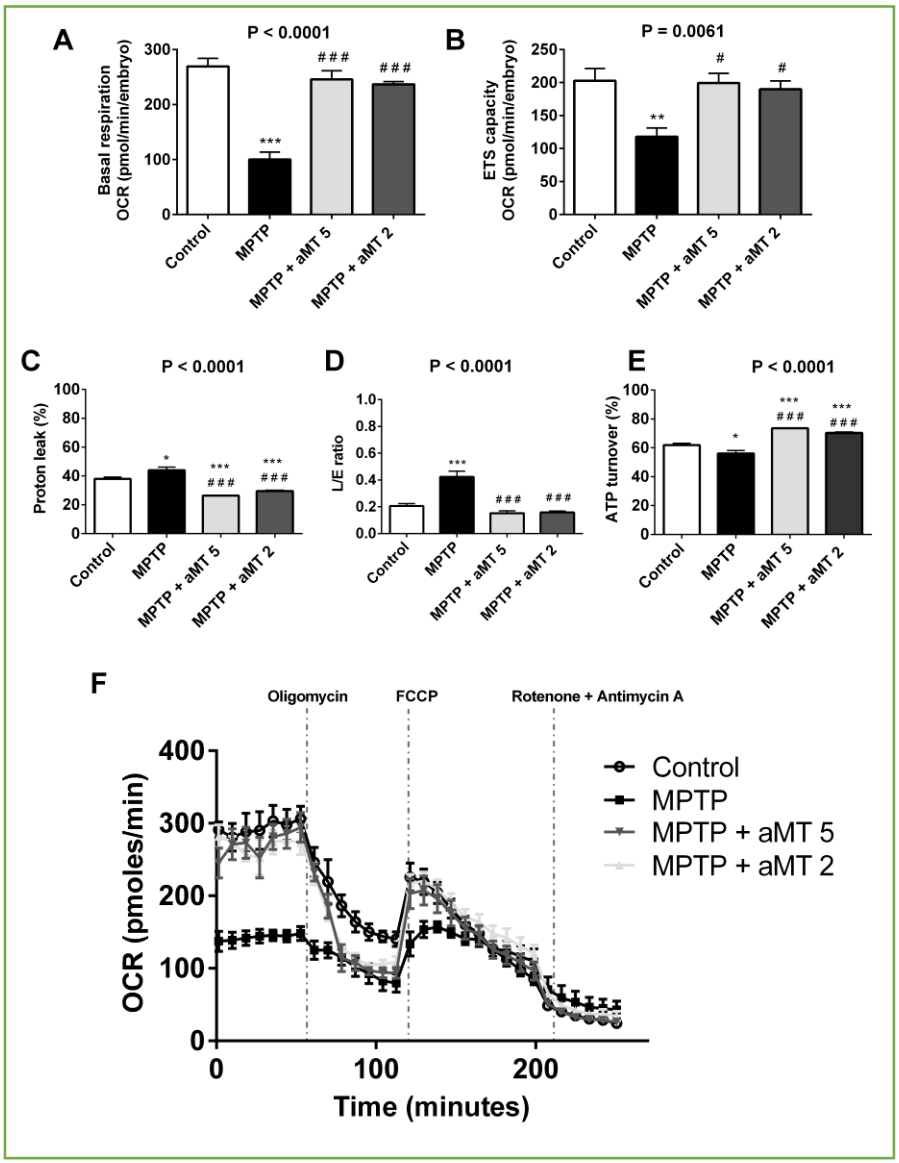

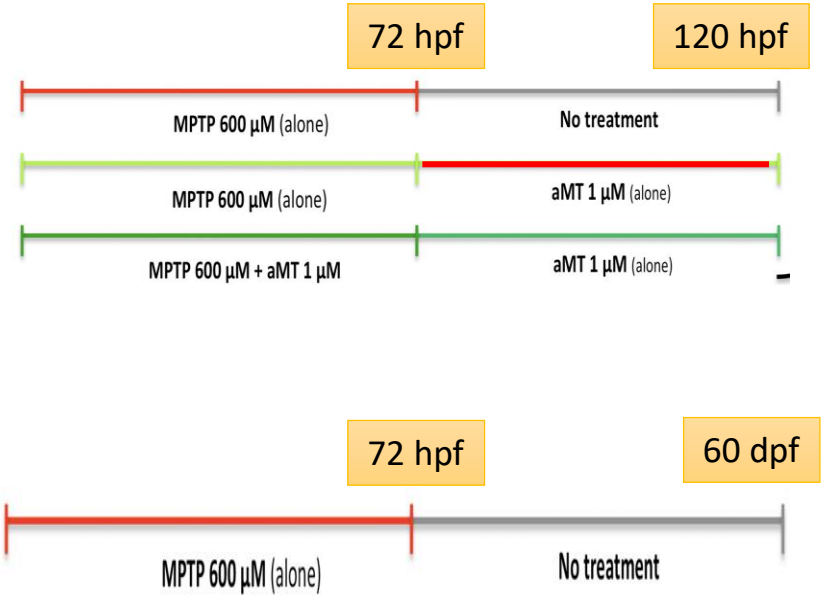

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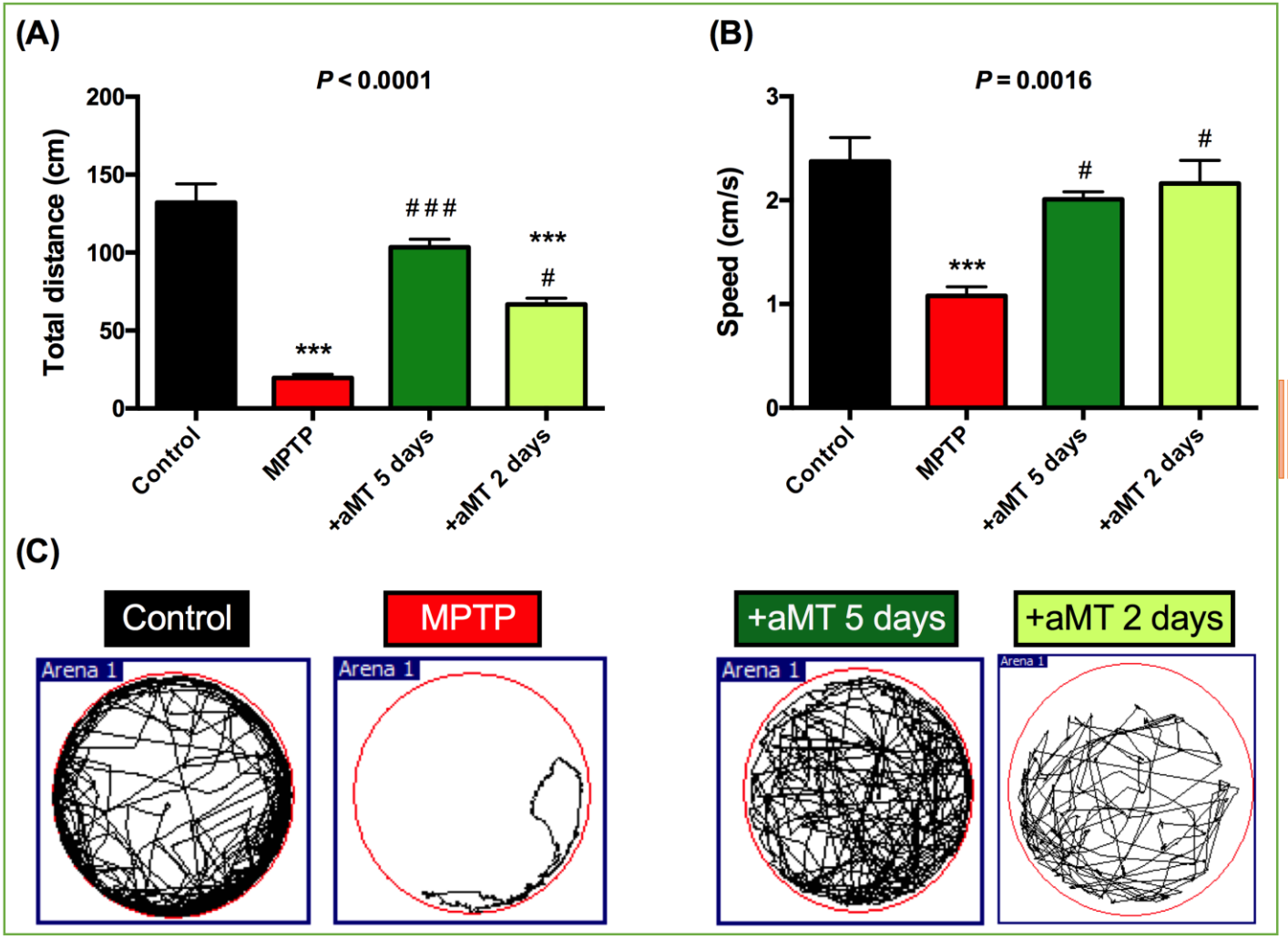
RECOVERS MIOTOCHONDRIAL BIOENERGETIC FUNCTION

Diaz-Casado E et al. J Pineal Res 2016; doi:10.1111/jpi.12332
Diaz-Casado E et al. Zebrafish 2018; doi:10.1089/zeb.2017.1479



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RECOVERS MOTOR PERFORMANCE

Diaz-Casado E et al. J Pineal Res 2016; doi:10.1111/jpi.12332
Diaz-Casado E et al. Zebrafish 2018; doi:10.1089/zeb.2017.1479

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