



# MELATONINA, DIABETES MELLITUS E SUAS COMPLICAÇÕES

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Prof. Dr. Klausen Oliveira Abreu

# Diabetes mellitus

- Egípcios
  - Perda de peso e poliúria
- Gregos
  - Diabetes – “passar através”
  - Mellitus – mel (latina)
- 425 milhões de pessoas no mundo (IDF)
  - Maior epidemia global do século 21
  - 12% das despesas globais com saúde – 727 bilhões de dólares



# Diabetes mellitus

## Tipo 1 (insulinodependente)

- 5-10% dos diabéticos
- Doença genética\* do sistema imune
- Deficiência de insulina
- Surge normalmente na infância e abaixo dos 35 anos

## Tipo 2

- 90% dos diabéticos
- Doença complexa
- Incidência aumenta com a idade
- Combinação de deficiência e resistência à insulina

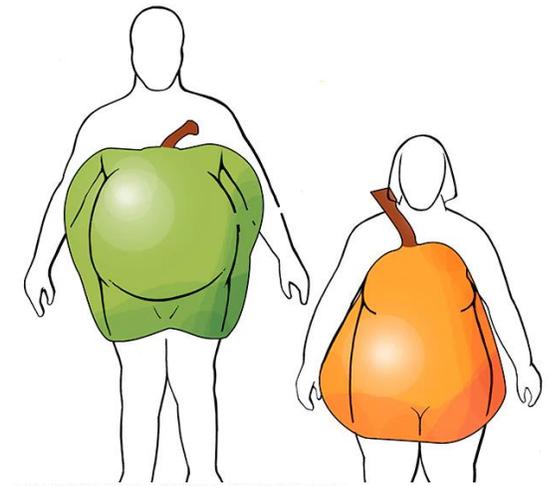
# Diabetes mellitus – tipo 2

## Deficiência à insulina

- Progressiva
- Não mediada pelo sistema imune
- Exaustão das células beta  
(hipersecreção), toxicidade pela glicose  
e lipídeos ou fatores genéticos

## Resistência à insulina

- Anormalidades no receptor de insulina
- Anormalidades genéticas nas enzimas
- Obesidade (central)
- Sedentarismo

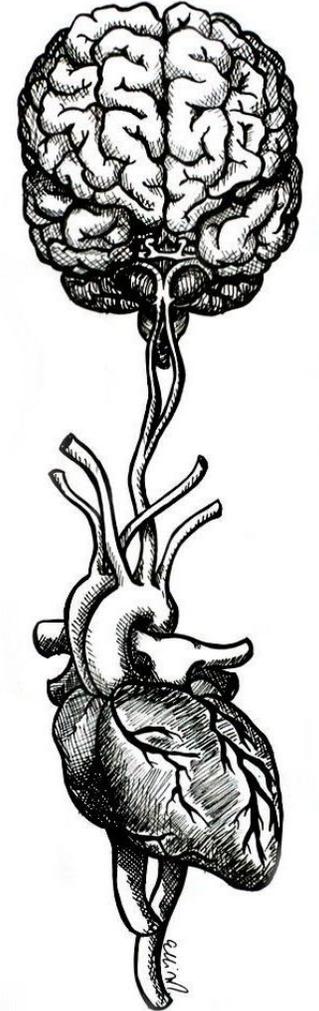


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# Alterações patológicas

## Macrovasculares

- Aterosclerose nas artérias coronárias
- AVE
- Doenças coronarianas
- Doença vascular periférica



# Complicações do DM

## Microvasculares

- Retinopatia
  - Cegueira
  - Espessamento da retina
- Nefropatia
  - Diálise ou transplante
  - Metabolismo dos lipídeos e estresse oxidativo
- Neuropatia



# Neuropatia diabética

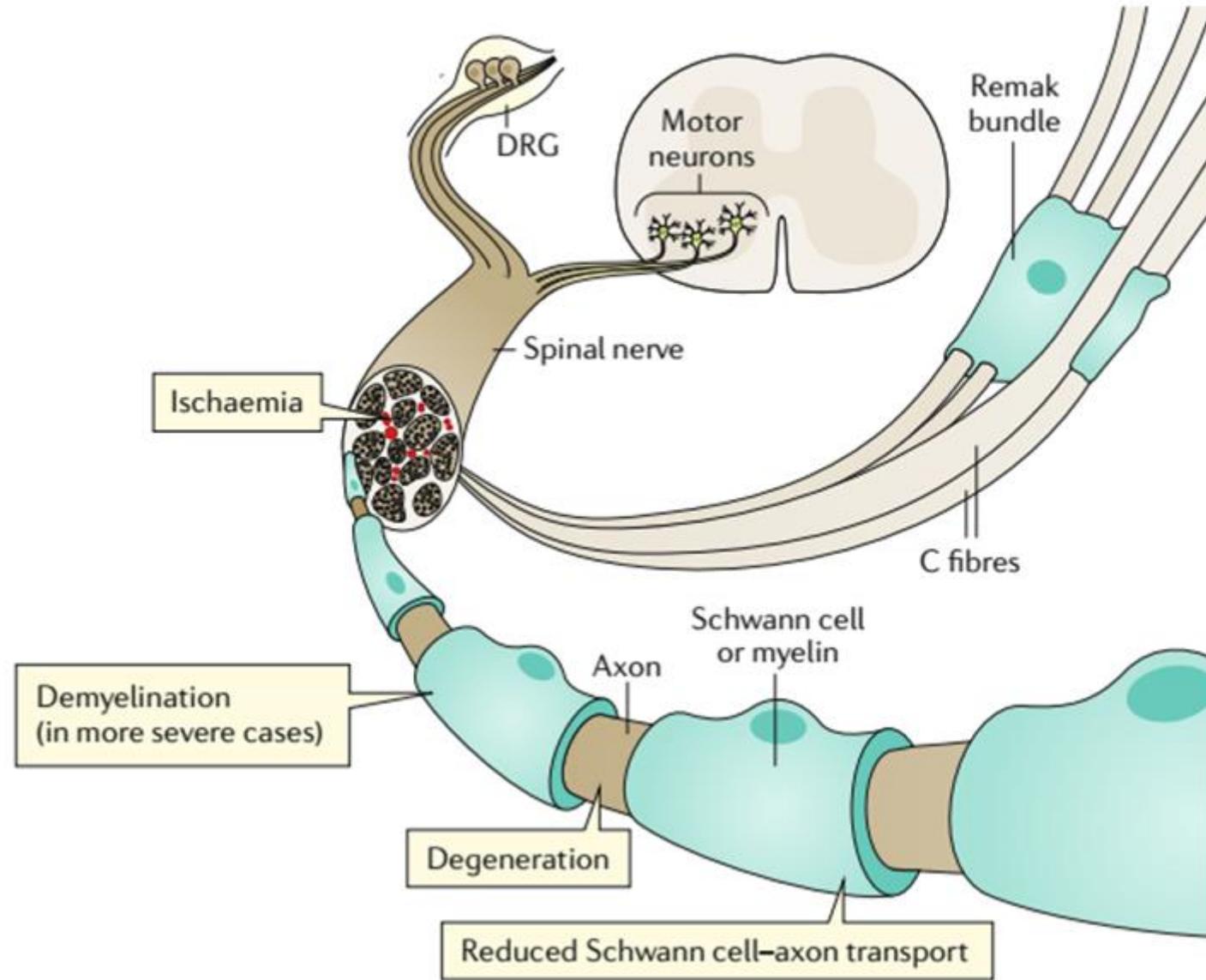
Conjunto de síndromes causadas por danos ao sistema nervoso

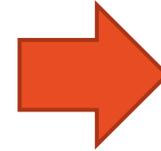
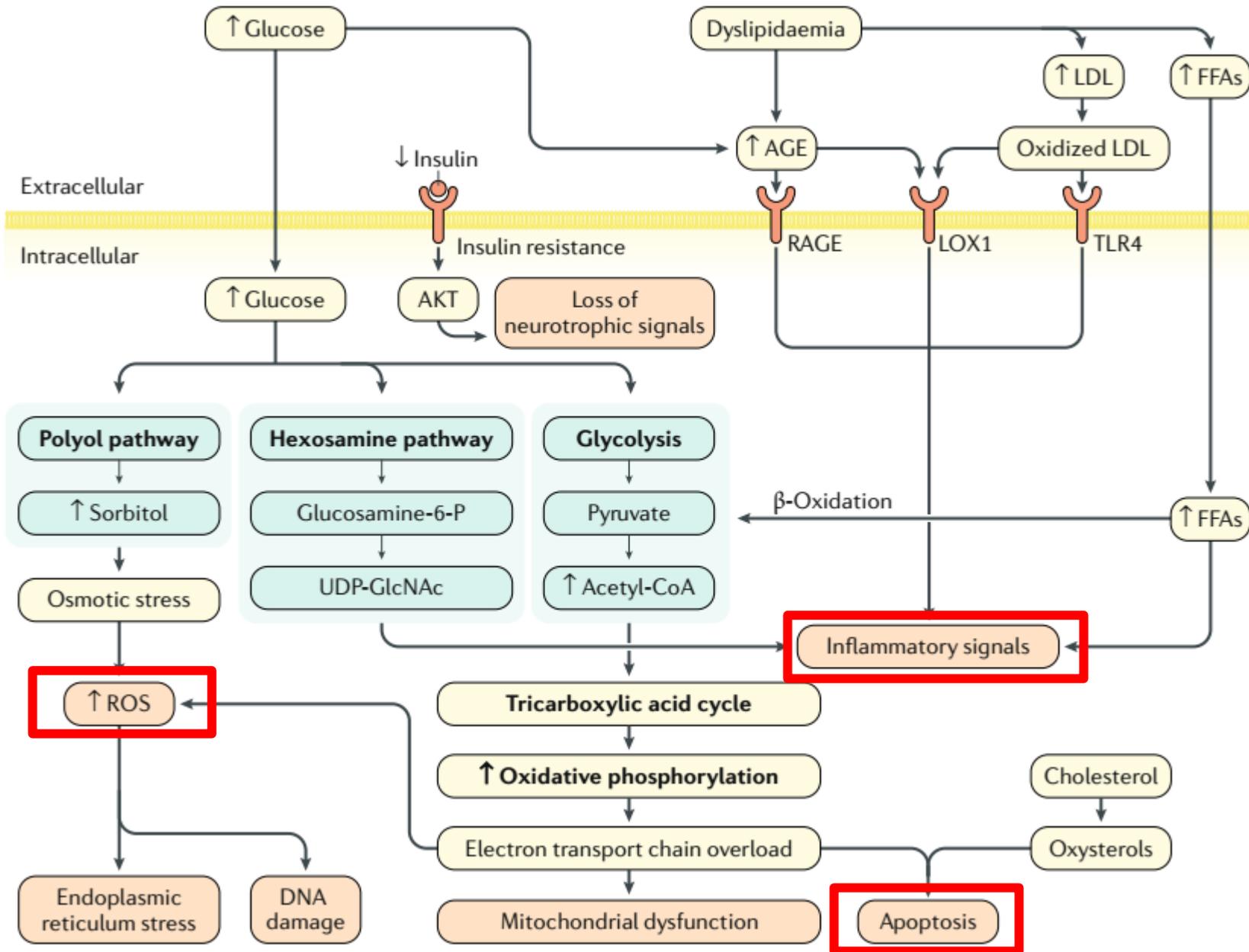
50% dos pacientes com DM

Redução da qualidade de vida

Aumento do risco de quedas, dor, fraqueza, incoordenação

Alteração da percepção térmica, dor, toque e vibração

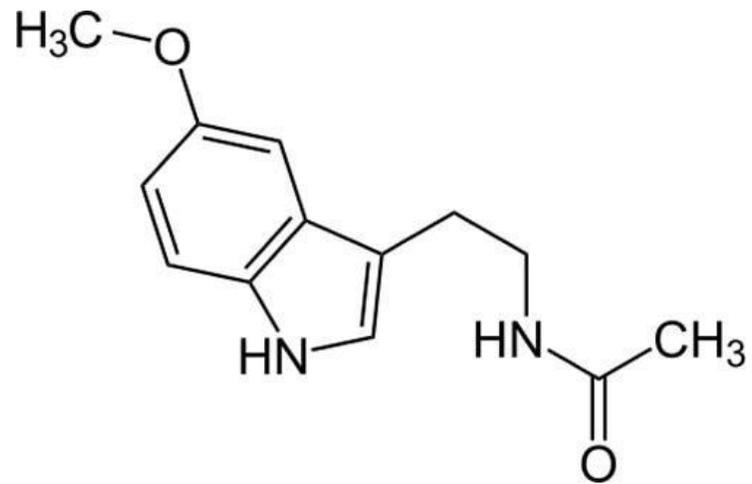




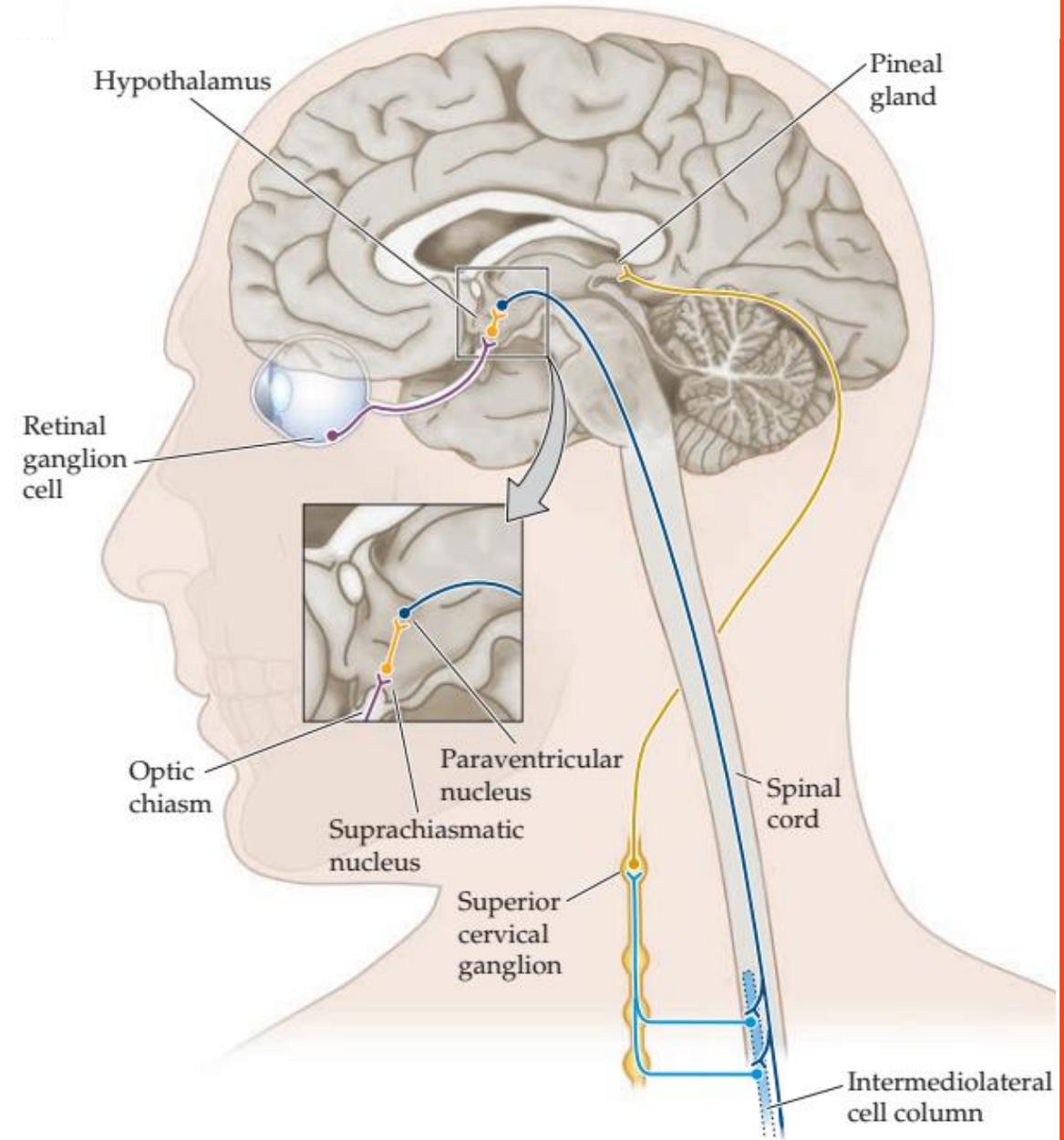
**MELATONINA**

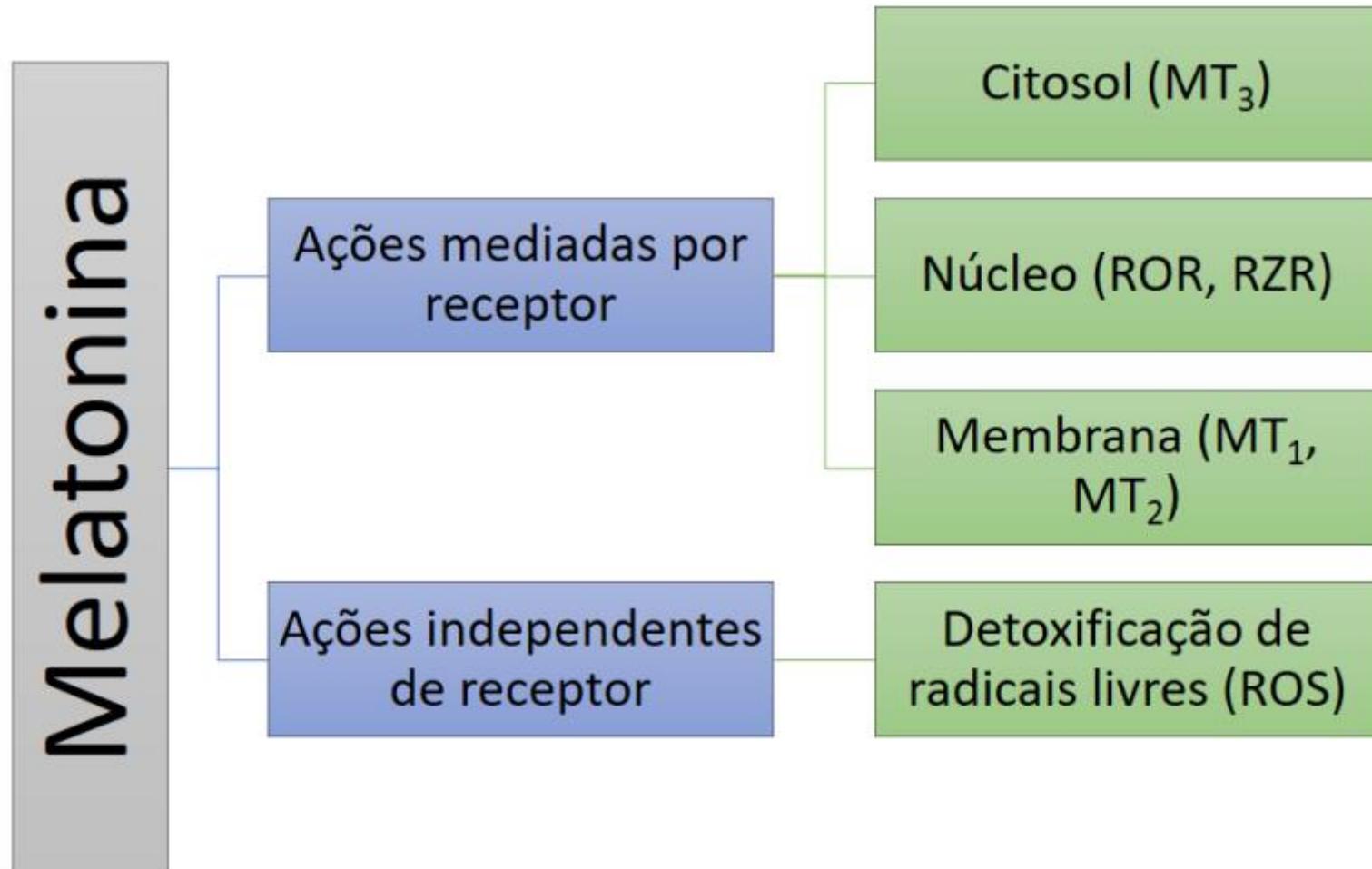
# Melatonina

N-acetil-5-metoxitriptamina

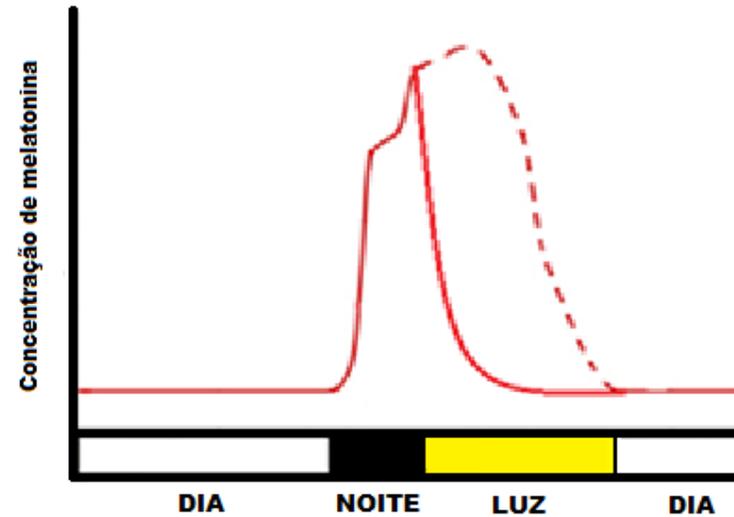
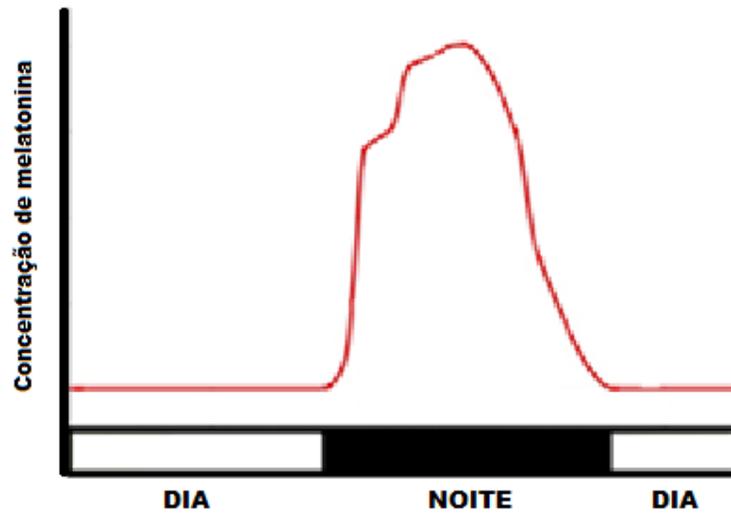


Estrutura química da melatonina



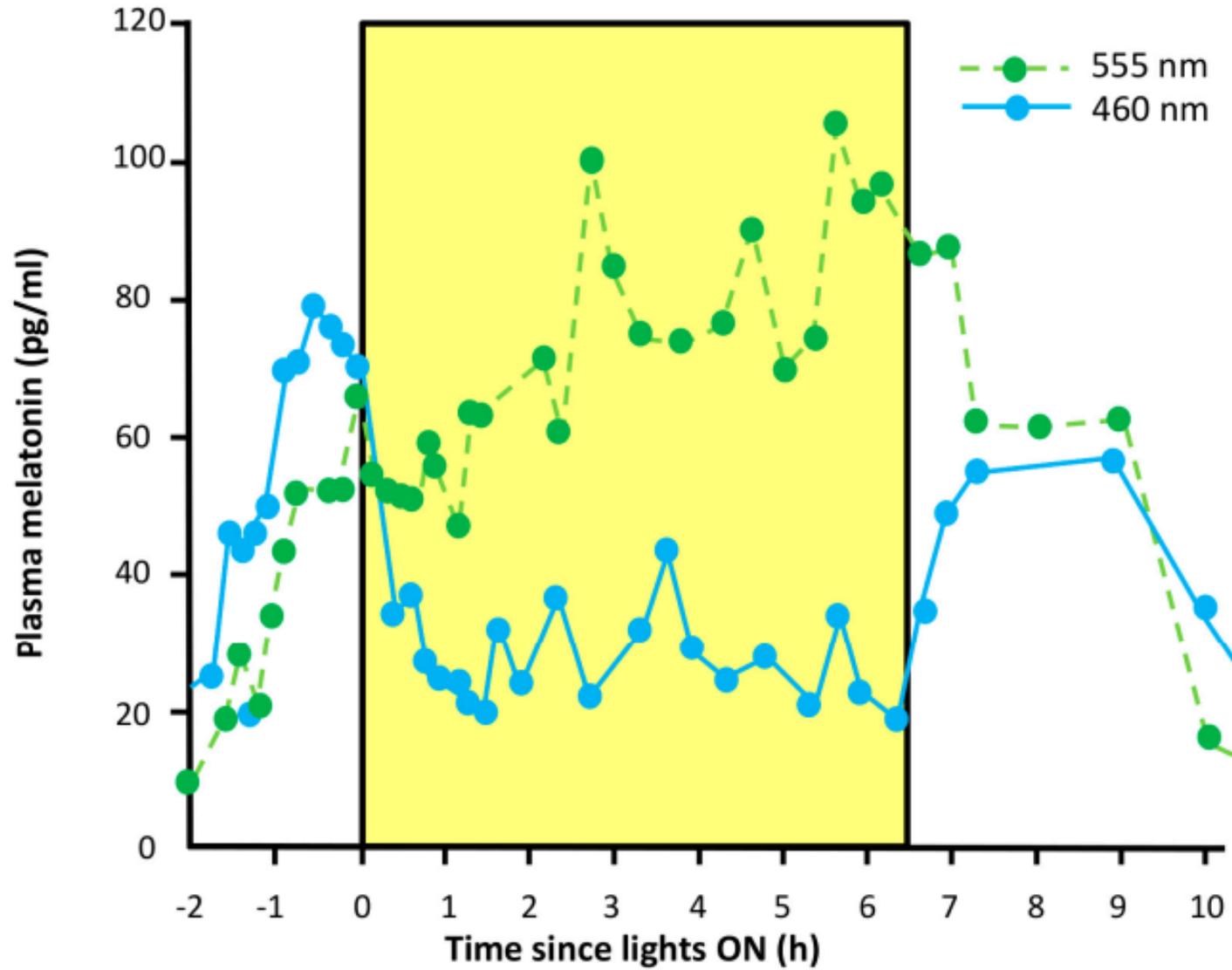


# Melatonina



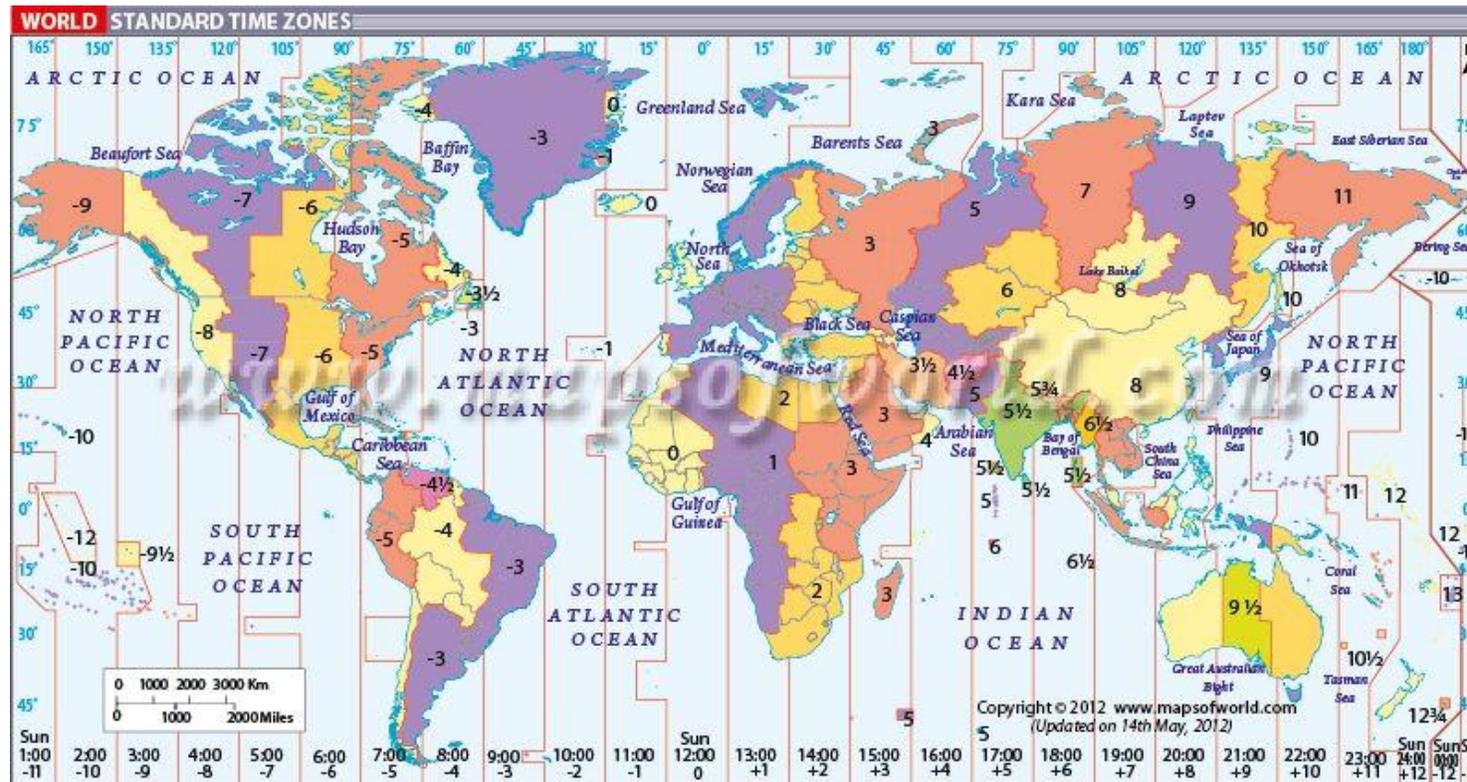
Inibição da síntese de melatonina pela luz

ARENDRT et al., (1988)



BONMATI-CARRION et al., (2014)

# Jet lag

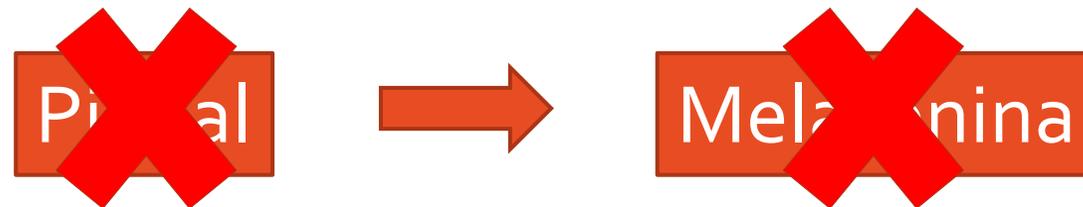


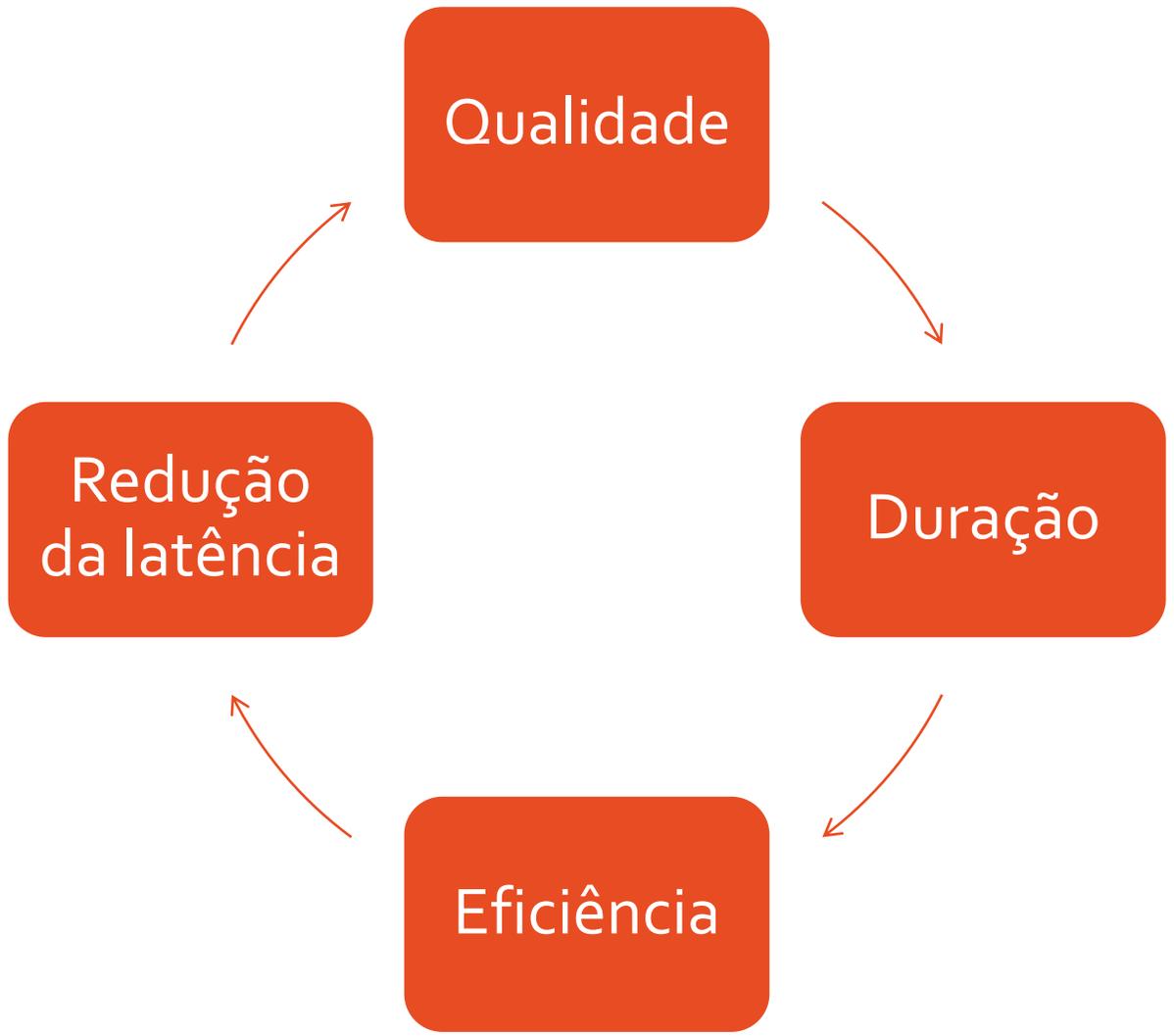
- Fadiga
- Mal-estar
- Distúrbios de sono

# Distúrbios do sono

## Pinealectomizados

- Redução do sono total
- Despertares noturnos
- Baixa qualidade do sono



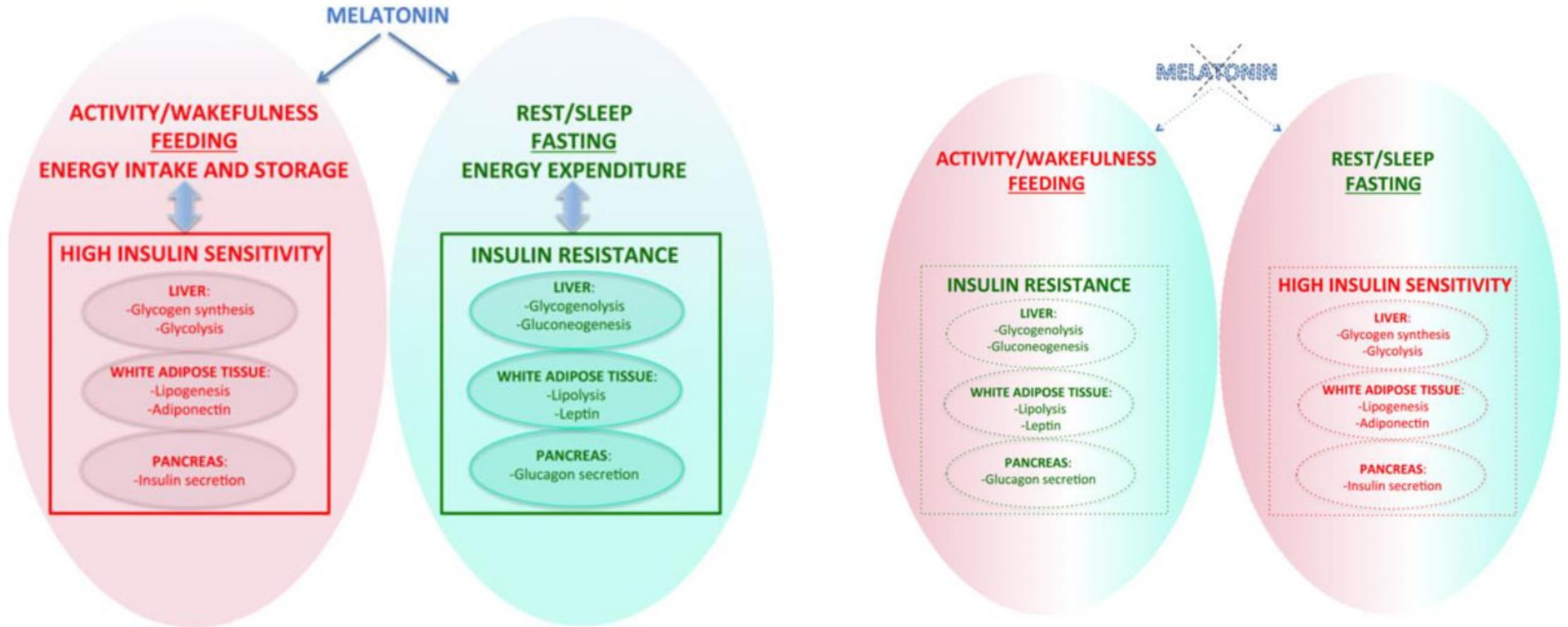


## Baixa toxicidade

- Ratos
  - 0,5-5 mg/kg (maioria)
  - 800 mg/kg
- Humanos
  - 0,5-10 mg/kg (recém nascidos)
  - 0,1 – 300 mg/kg/d (adultos/idosos)

# A MELATONINA E O METABOLISMO ENERGÉTICO

Diabetes mellitus



# Melatonina e metabolismo energético

## Infusão de extratos da pineal

- Hipoglicemia
- Aumento da tolerância à glicose

## Pinealectomia – “síndrome diabetogênica”

- Intolerância à glicose
- Resistência à insulina periférica e central
- Redução da expressão gênica do GLUT<sub>4</sub> (TAB, músculo cardíaco e esquelético)

# Melatonina e metabolismo energético

## High Fat Diet (HFD)

- Redução da sensibilidade à insulina
- Redução da tolerância à glicose
- Inflamação de baixo grau

## Ilhotas pancreáticas

- $MT_1$  e  $MT_2$  – redução da secreção de insulina estimulada pela glicose

## Fêmeas prenhas pinealectomizadas

- Prole desenvolve intolerância à glicose, resistência à insulina e danos na produção de insulina

# Melatonina e metabolismo energético

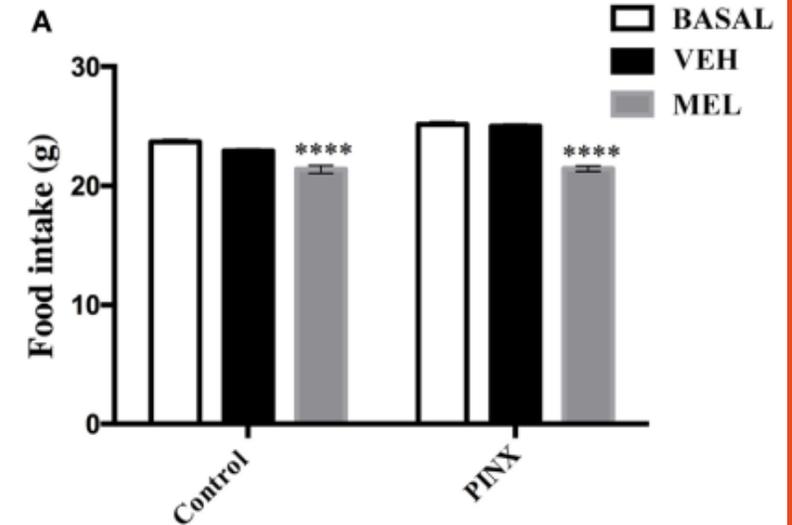
MEL (icv) reduz ingestão

MT<sub>1</sub> KO camundongo

- Resistência sistêmica à insulina

MT<sub>2</sub> KO (fêmeas)

- Redução da sensibilidade à insulina hepática
- Aumento da secreção de insulina



# MELATONINA E DIABETES MELLITUS

Consequências do DM sobre a glândula pineal

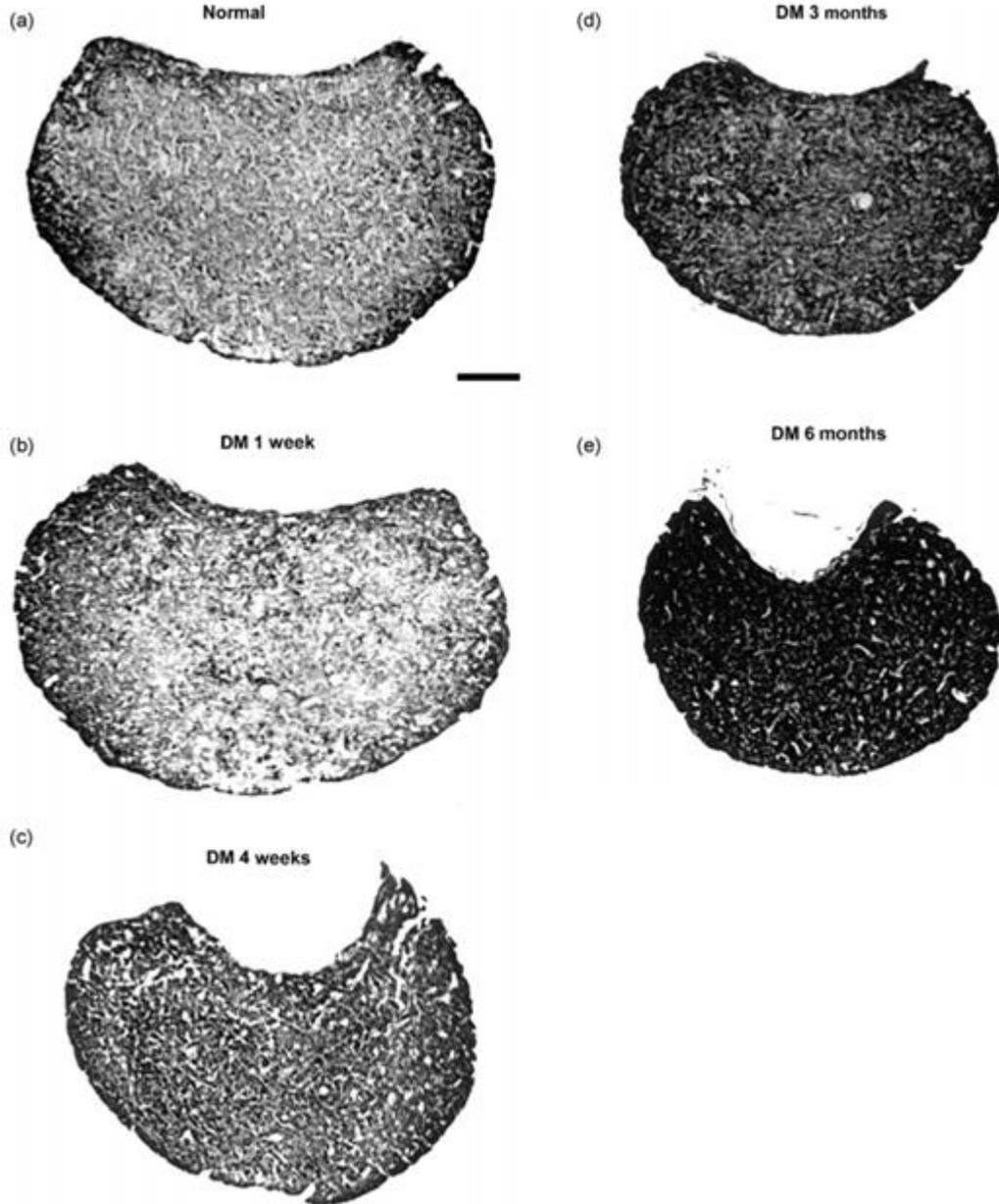
# Expression of protein gene product 9.5, tyrosine hydroxylase and serotonin in the pineal gland of rats with streptozotocin-induced diabetes

Mang-Hung Tsai<sup>a</sup>, I-Hua Wei<sup>a</sup>, Ya-Fen Jiang-Shieh<sup>b</sup>,  
Ming-Jia Jou<sup>a</sup>, Miao-Hwa Ko<sup>a</sup>, Hui-Min Chen<sup>c</sup>, Ching-Hsiang Wu<sup>d,\*</sup>

and nuclear diameter of pinealocytes in different experimental time periods of the control and diabetic rats

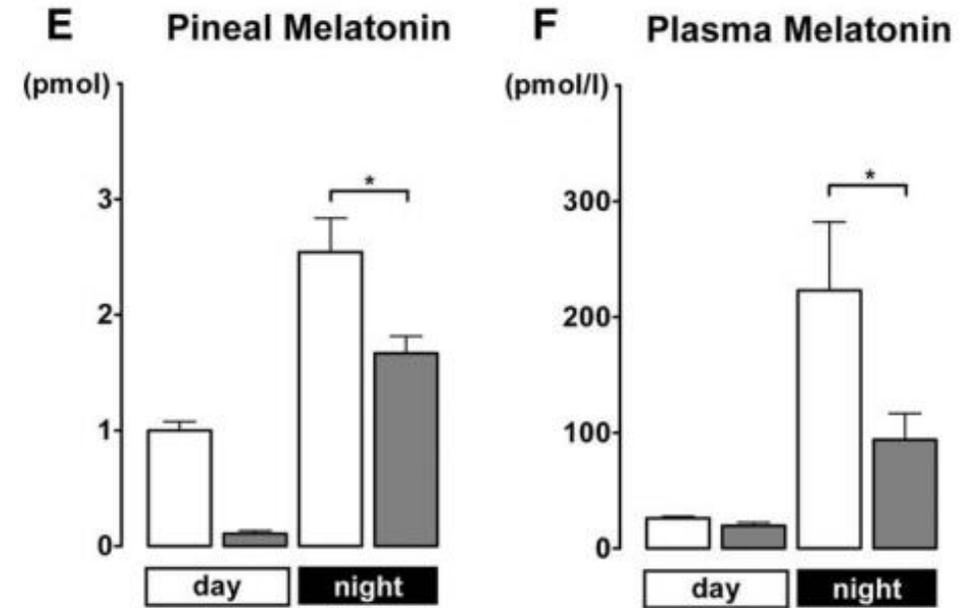
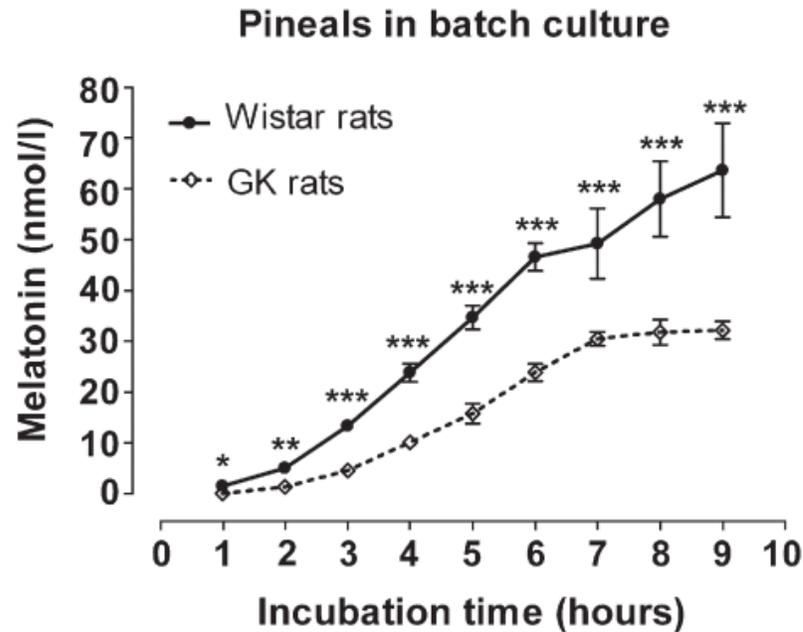
Pineal volume (mm <sup>3</sup> )	Total cell number (×10 <sup>6</sup> )	Nuclear diameter (μm)
0.79 ± 0.05	3.8 ± 0.29	7.39 ± 0.79
0.84 ± 0.06	3.6 ± 0.38	7.41 ± 0.81
0.86 ± 0.03	3.5 ± 0.66	7.40 ± 0.69
0.91 ± 0.04	3.1 ± 0.54	7.37 ± 0.55
0.89 ± 0.07	2.8 ± 0.57	7.44 ± 0.61 <sup>a</sup>
0.81 ± 0.06	3.9 ± 0.49	7.42 ± 0.68
0.82 ± 0.03	3.8 ± 0.39	7.35 ± 0.56
0.62 ± 0.06*	3.4 ± 0.55	7.06 ± 0.36*
0.51 ± 0.08*	3.1 ± 0.76	7.02 ± 0.45*
0.53 ± 0.11*	2.9 ± 0.69	6.86 ± 0.32 <sup>*,a</sup>

of diabetes.



## Pineal melatonin synthesis is decreased in type 2 diabetic Goto-Kakizaki rats

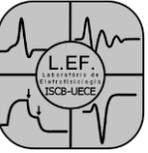
Thomas Frese<sup>a</sup>, Andreas Gunter Bach<sup>a,\*</sup>, Eckhard Mühlbauer<sup>b</sup>, Klaus Pönicke<sup>c</sup>, Hans-Jürgen Brömme<sup>d</sup>, André Welp<sup>a</sup>, Elmar Peschke<sup>a</sup>



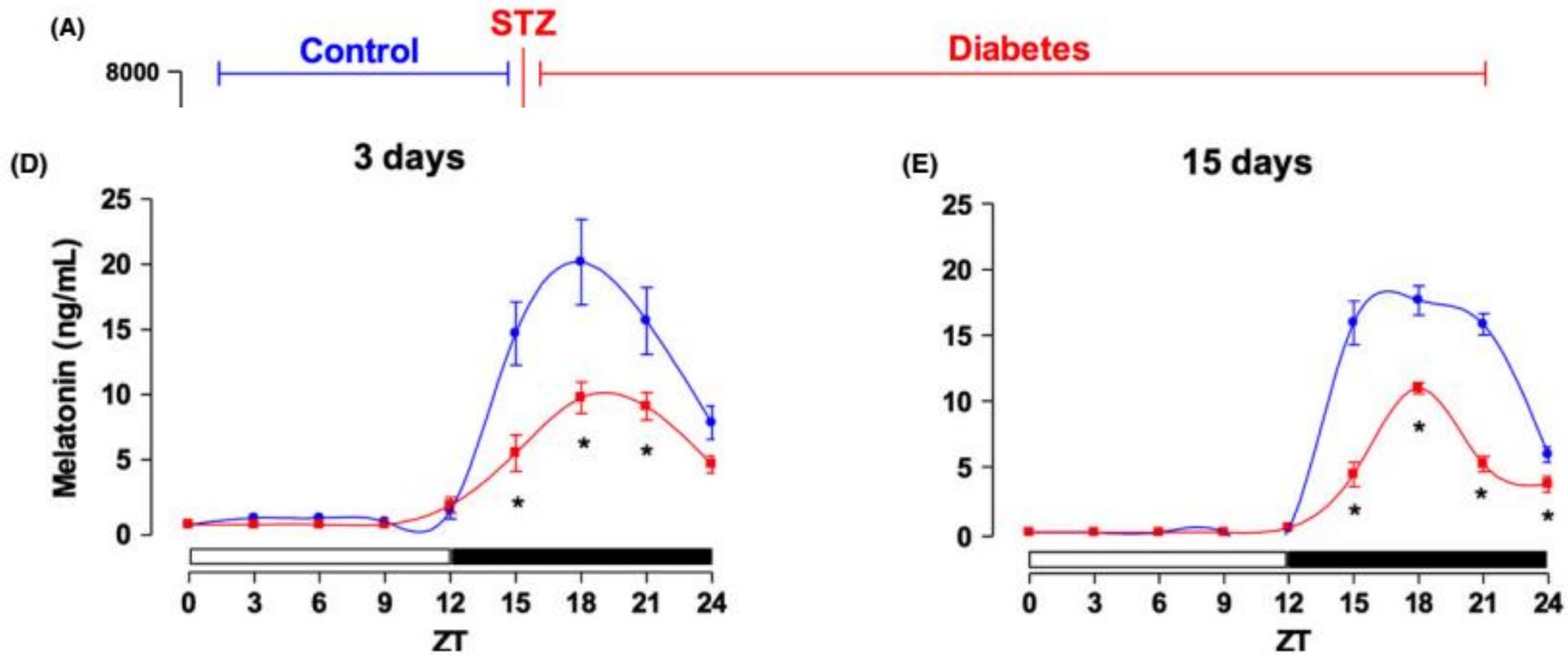
**Fig. 4.** In vitro melatonin secretion of pineal glands (1 pineal per batch) of 8-week-old Wistar rats (solid line) and GK rats (broken line), while under incubation with 1  $\mu$ M noradrenaline. Data are means  $\pm$  SEM of  $n = 8$  batches per group (\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ ).

## Em síntese...

Os ratos diabéticos GK produzem menos melatonina em reação à noradrenalina in vitro. As modificações no processo de síntese de melatonina podem ser resultado de neuropatia diabética da glândula pineal e suas inervações simpáticas.



## Melatonin synthesis impairment as a new deleterious outcome of diabetes-derived hyperglycemia



# MELATONINA E DIABETES MELLITUS

Efeitos do tratamento com melatonina sobre a neuropatia diabética – Sistema Nervoso Central

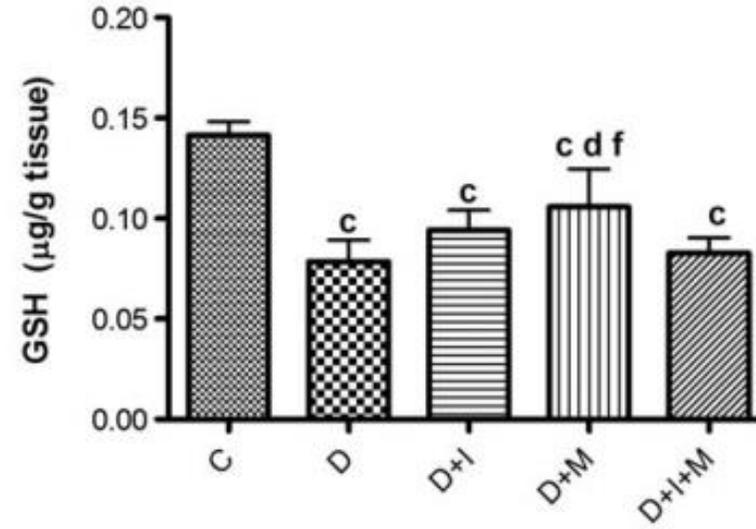
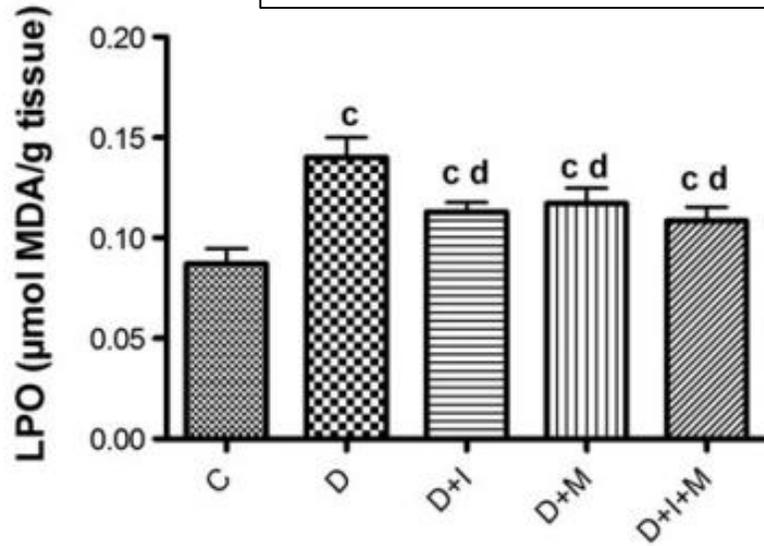
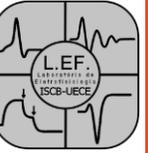
# Melatonin improves hyperglycemia induced damages in rat brain

Begum Gurel-Gokmen<sup>1</sup> | Hazal Ipekci<sup>1</sup> | Sehkar Oktay<sup>1</sup> | Burcin Alev<sup>1</sup> |  
 Unsal Veli Ustundag<sup>1</sup> | Esin Ak<sup>2</sup> | Dilek Akakin<sup>3</sup> | Goksel Sener<sup>4</sup> | Ebru Emekli-Alturfan<sup>1</sup> |  
 Aysen Yarat<sup>1</sup> | Tugba Tunali-Akbay<sup>1</sup>

**TABLE 1** Body weights and blood glucose levels in all groups

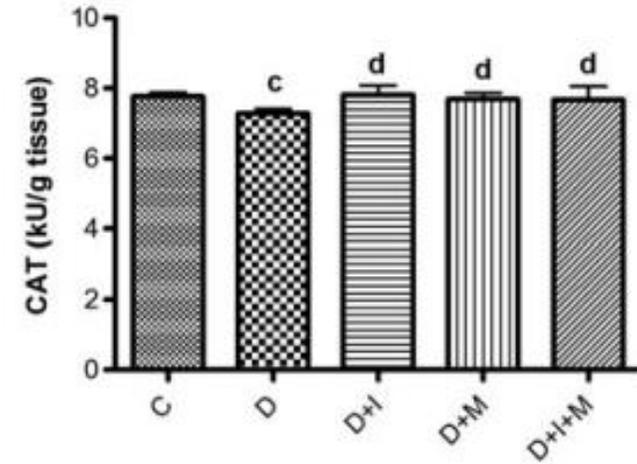
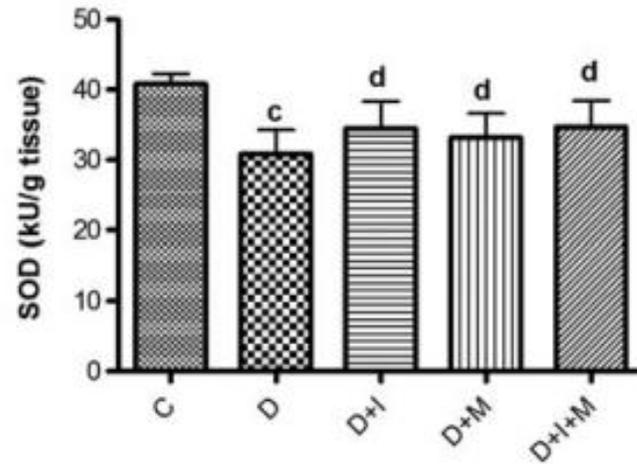
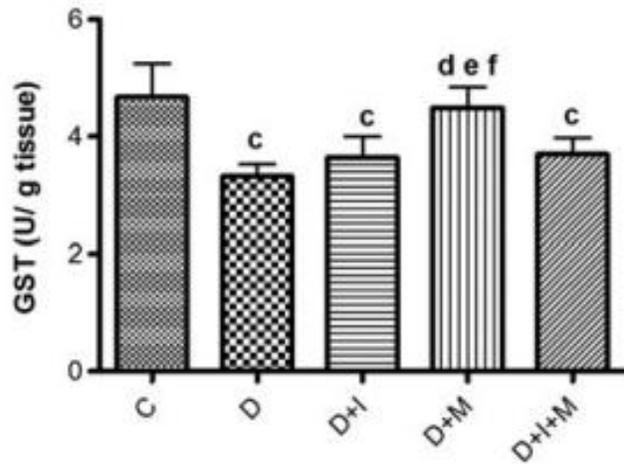
		C (n = 8)	D (n = 10)	D + I (n = 10)	D + M (n = 10)	D + I + M (n = 10)
Body weight(g)	Day 0	290 ± 2.5	292 ± 1.7	289.9 ± 3.7	290 ± 4.6	292 ± 1.8
	Day 84	303 ± 3.7 <sup>a</sup>	232 ± 2.8 <sup>a,c</sup>	284 ± 5.3 <sup>c,d,f</sup>	290 ± 4.8 <sup>c,d,e,f</sup>	309.9 ± 5.2 <sup>a,c,d,e,f</sup>
Blood glucose levels(mg/dL)	Day 2	94 ± 0.3	321 ± 11.4 <sup>c</sup>	345 ± 15.4 <sup>c,d,f</sup>	301 ± 12.1 <sup>c,d,e,f</sup>	320 ± 5.1 <sup>c,e</sup>
	Day 84	89 ± 3.2 <sup>b</sup>	365 ± 20.1 <sup>b,c</sup>	125 ± 6.3 <sup>b,c,d,e,f</sup>	197 ± 4.9 <sup>b,c,d,e</sup>	170 ± 3.2 <sup>b,c,d,e</sup>

# Biomarcadores de desequilíbrio oxidante e antioxidante



Peroxidação lipídica

Glutationa

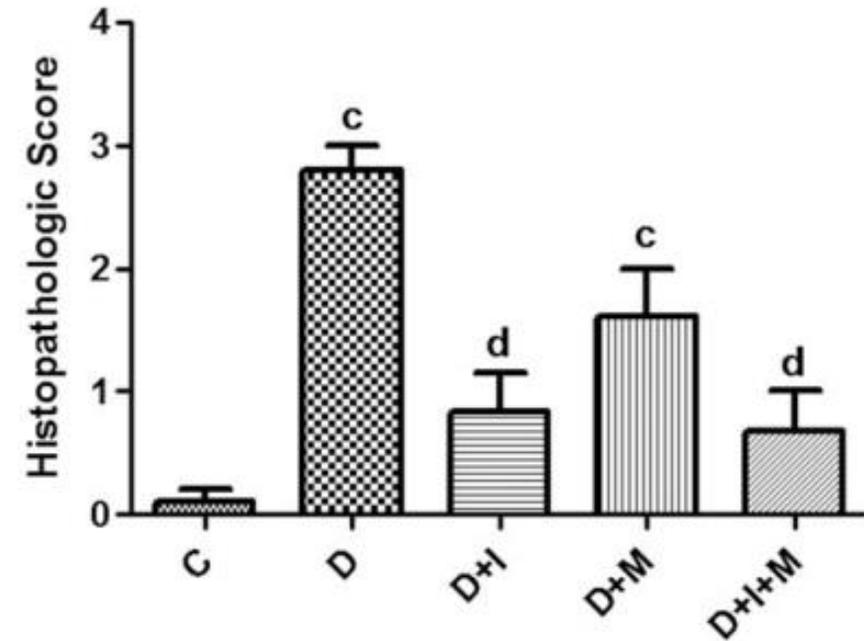


Glutationa-s-transferase

Superóxido dismutase

Catalase

Escores histopatológicos do córtex



**FIGURE 3** Photomicrographs of cortex and histopathological scores. A: Control group, 3B: Diabetes group, C: Diabetes + Insulin group, D: Diabetes + Melatonin group, E: Diabetes + Insulin + Melatonin group. Normal cortical morphology of neuropil and neurons (arrow) with large nuclei and prominent nucleoli were observed in the control group. Severely degenerated neurons (arrowheads) observed with shrunken cytoplasm and pyknotic nuclei in the D group decreased in the Insulin- and Insulin + Melatonin-treated groups. Few degenerated neurons (arrowhead) were observed in the Melatonin-treated group. Arrows: Normal appearing neurons, arrowheads: degenerated neurons. Scale bar, 20  $\mu$ m. C: Control, D: Diabetes, D + I: Diabetes + Insulin, D + M: Diabetes + Melatonin, D + I + M: Diabetes + Insulin + Melatonin. C:  $P < 0.05$  compared with group C, D:  $P < 0.05$  compared with group D

## Em síntese...

A melatonina melhorou os danos causados pelo DM em tecido cerebral, diminuindo a glicemia e neutralizando a produção de ROS.

# Potential therapeutic role of melatonin on STZ-induced diabetic central neuropathy: A biochemical, histopathological, immunohistochemical and ultrastructural study



Mohamed M.M. Metwally<sup>a,1</sup>, Lamiaa L.M. Ebraheim<sup>b,1</sup>, Azza A.A. Galal<sup>c,\*,1</sup>

**Table 1**

The effect of IP administration of Mel (50 mg/kg/day) for 45 days on the body weight in adult male rats with STZ-induced type 1 diabetes.

Parameters	Normal control	Vehicle control	Mel	diabetic	diabetic-Mel
Initial body weights (g)	258.00 ± 2.26	255.23 ± 2.87	257.33 ± 2.85	260.50 ± 2.83	259.17 ± 2.57
Final body weights (g)	287.83 ± 2.53 <sup>a</sup>	290.89 ± 4.23 <sup>a</sup>	288.17 ± 2.35 <sup>a</sup>	187.17 ± 2.12 <sup>c</sup>	199.50 ± 3.10 <sup>b</sup>

**Table 2**

The effect of IP administration of Mel (50 mg/kg/day) for 45 days on BGL in adult male rats with STZ- induced type 1 diabetes.

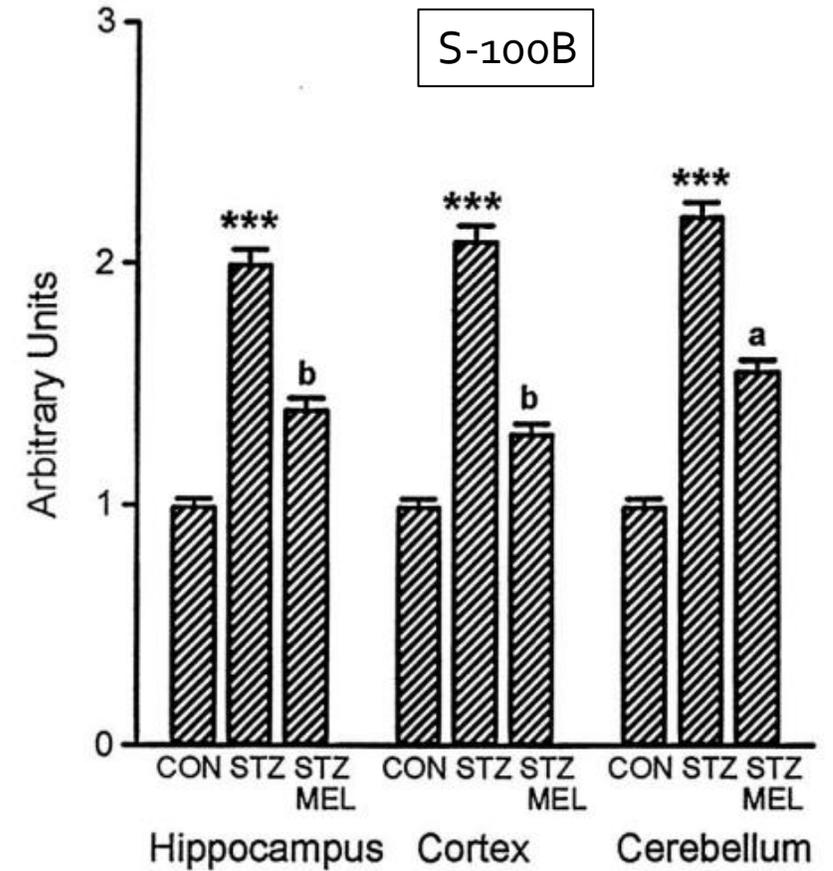
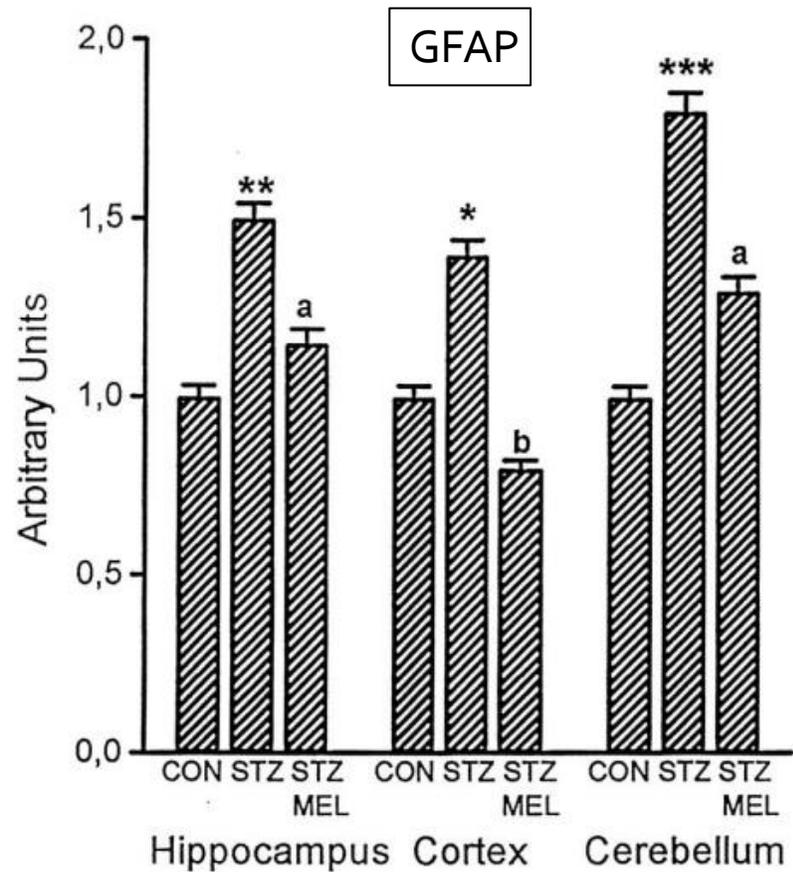
	Normal control	Vehicle control	Mel	diabetic	diabetic-Mel
Initial BGL (mg/dL)	121.33 ± 3.63	120.54 ± 2.71	118.83 ± 2.79	118.67 ± 3.16	119.50 ± 2.96
Final BGL (mg/dL)	118.33 ± 2.95 <sup>b</sup>	121.98 ± 4.25 <sup>b</sup>	118.67 ± 2.45 <sup>b</sup>	316.17 ± 19.41 <sup>a</sup>	308.67 ± 17.68 <sup>a</sup>

**Table 3**

The effect of IP administration of Mel (50 mg/kg/day) for 45 days on the activities of the antioxidant enzymes and lipid peroxidation in the cerebral cortices, liver, and kidneys in adult male rats with STZ- induced type 1 diabetes.

Parameters	Normal control	Vehicle control	Mel		diabetic		diabetic-Mel
Cerebral cortex							
CAT (U/mg protein)	5.67 ± 0.06 <sup>a</sup>	5.52 ± 0.04 <sup>a</sup>	5.69 ± 0.08 <sup>a</sup>		4.15 ± 0.02 <sup>c</sup>		4.93 ± 0.03 <sup>b</sup>
SOD (U/mg protein)	4.23 ± 0.05 <sup>a</sup>	4.43 ± 0.09 <sup>a</sup>	4.35 ± 0.11 <sup>a</sup>		2.27 ± 0.07 <sup>c</sup>		3.15 ± 0.04 <sup>b</sup>
GPx (U/mg protein)	2.19 ± 0.05 <sup>a</sup>	2.45 ± 0.11 <sup>a</sup>	2.29 ± 0.02 <sup>a</sup>		1.07 ± 0.02 <sup>c</sup>		1.59 ± 0.02 <sup>b</sup>
MDA (nmol/mg protein)	3.35 ± 0.04 <sup>c</sup>	3.83 ± 0.14 <sup>c</sup>	3.2 ± 0.03 <sup>c</sup>		5.7 ± 0.08 <sup>a</sup>		4.24 ± 0.05 <sup>b</sup>

MELATONIN REDUCES GLIAL REACTIVITY IN THE HIPPOCAMPUS,  
CORTEX, AND CEREBELLUM OF STREPTOZOTOCIN-INDUCED  
DIABETIC RATS



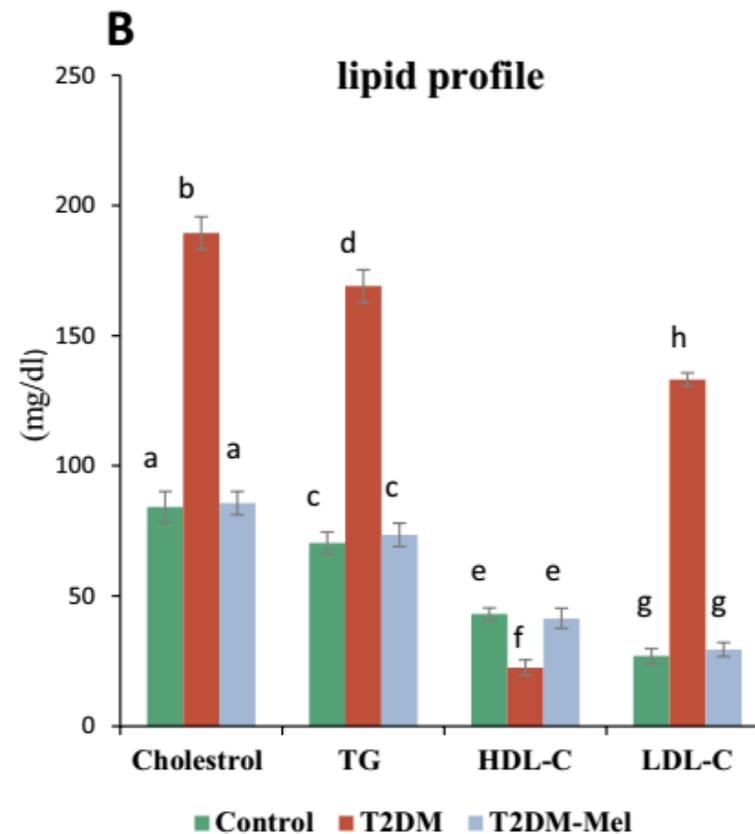
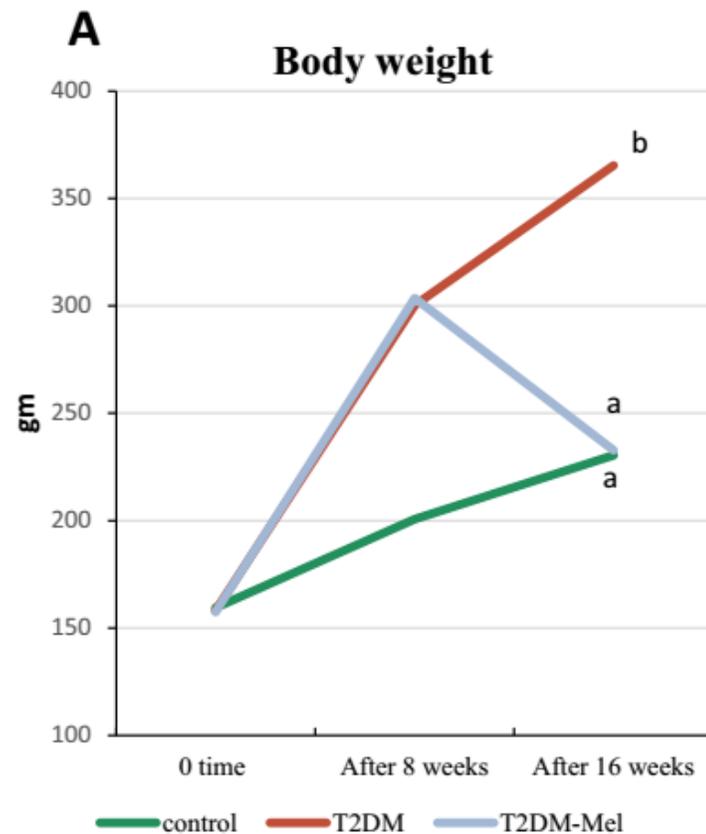
## Em síntese...

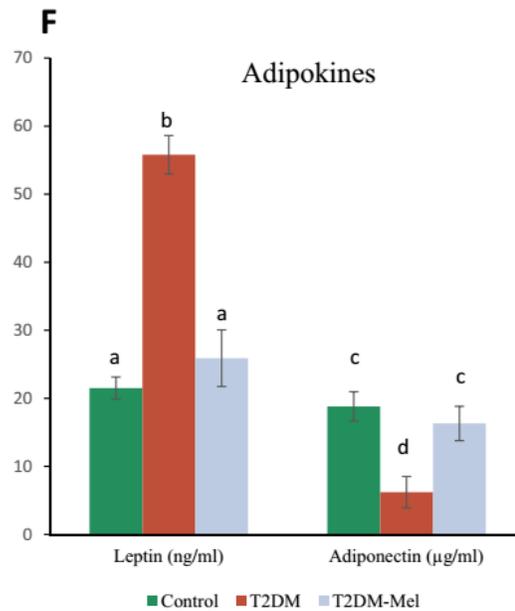
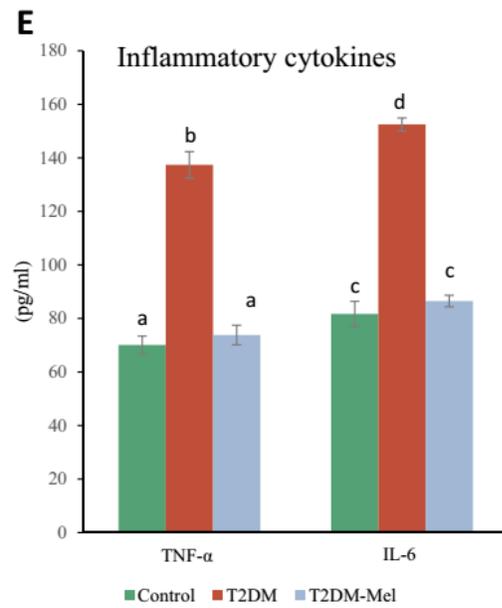
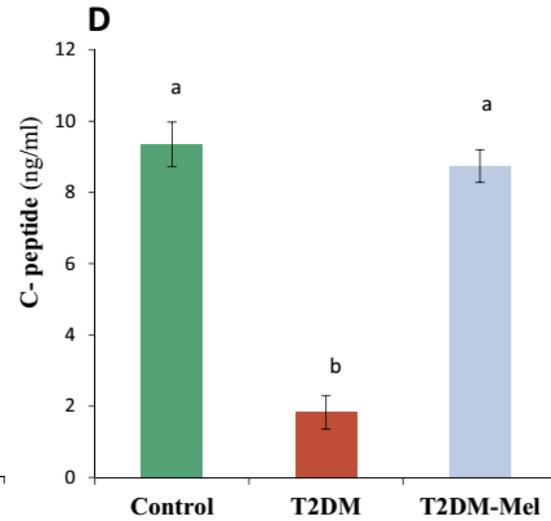
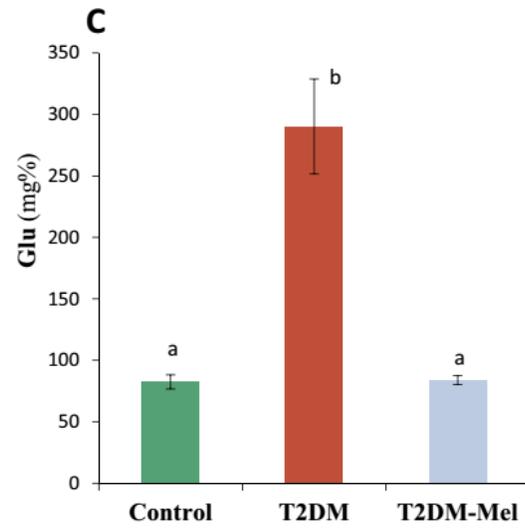
Além de fornecer proteção antioxidante direta aos neurônios, a melatonina pode fornecer neuroproteção por meio da supressão da reatividade glial e promoção do sistema de defesa antioxidante das células gliais.

# Exogenous melatonin restrains neuroinflammation in high fat diet induced diabetic rats through attenuating indoleamine 2,3-dioxygenase 1 expression

Adham M. Maher\*, Samar R. Saleh, Nihal M. Elguindy, Hagar M. Hashem, Galila A. Yacout

Biochemistry Department, Faculty of Science, Alexandria University, Alexandria 21511, Egypt





## Em síntese...

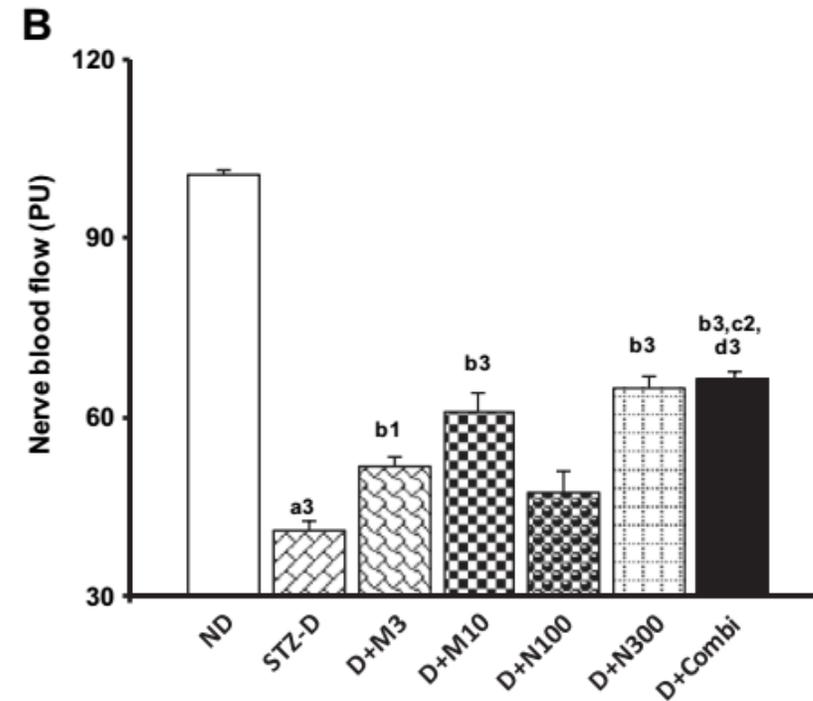
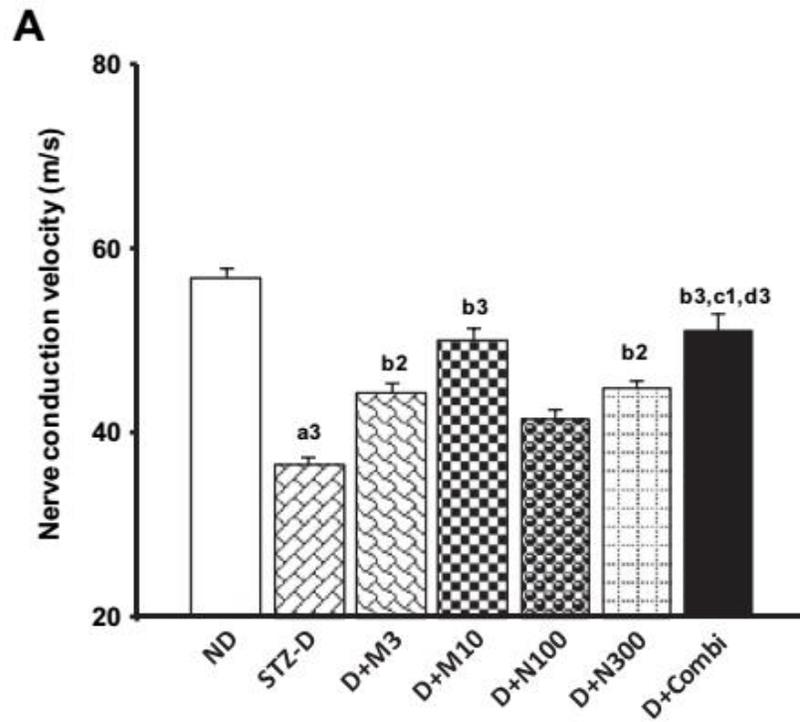
A melatonina pode interromper o desenvolvimento de neuroinflamação em ratos diabéticos por meio do seu efeito hipoglicemiante, aliviando o estado de dislipidemia.

# MELATONINA E DIABETES MELLITUS

Efeitos do tratamento com melatonina sobre a neuropatia diabética – sistema nervoso periférico e testes comportamentais

# Functional and biochemical evidence indicating beneficial effect of Melatonin and Nicotinamide alone and in combination in experimental diabetic neuropathy

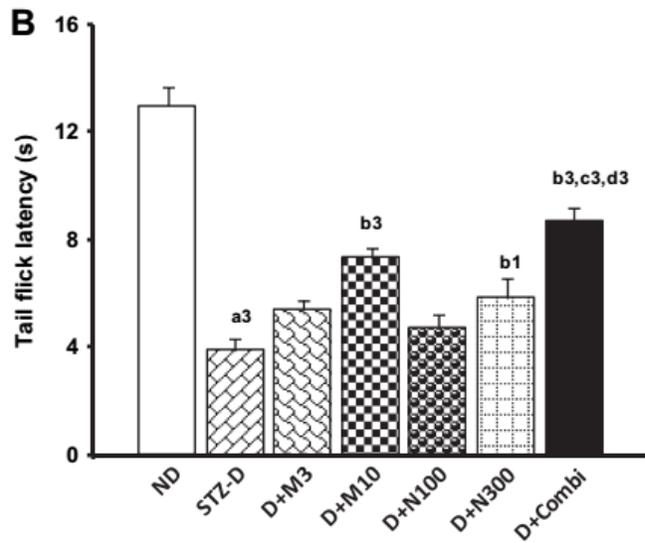
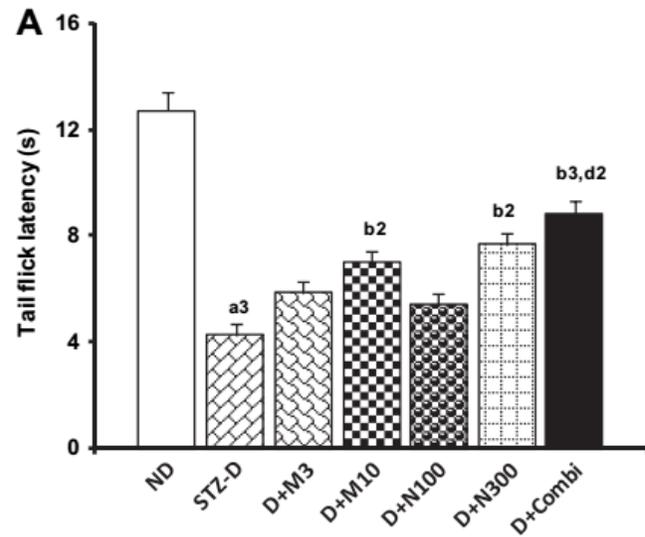
Geeta Negi<sup>a</sup>, Ashutosh Kumar<sup>a</sup>, Ravinder K. Kaundal<sup>a</sup>, Anil Gulati<sup>b</sup>, Shyam S. Sharma<sup>a,\*</sup>



## Em síntese...

A melatonina melhorou a velocidade de condução nervosa e o respectivo fluxo sanguíneo alterados pelo diabetes mellitus.

# Hiperalgnesia térmica



# MELATONINA E DIABETES MELLITUS

Perspectivas de utilização da melatonina

Research report

## Diabetes mellitus alters electrophysiological properties in neurons of superior cervical ganglion of rats

Nathalia Maria Silva-dos-Santos<sup>a</sup>, Klausen Oliveira-Abreu<sup>a</sup>, Luiz Moreira-Junior<sup>b</sup>, Tiago dos Santos-Nascimento<sup>c</sup>, Kerly Shamyra da Silva-Alves<sup>a</sup>, Andreлина Noronha Coelho-de-Souza<sup>a</sup>, Francisco Walber Ferreira-da-Silva<sup>a</sup>, José Henrique Leal-Cardoso<sup>a,\*</sup>

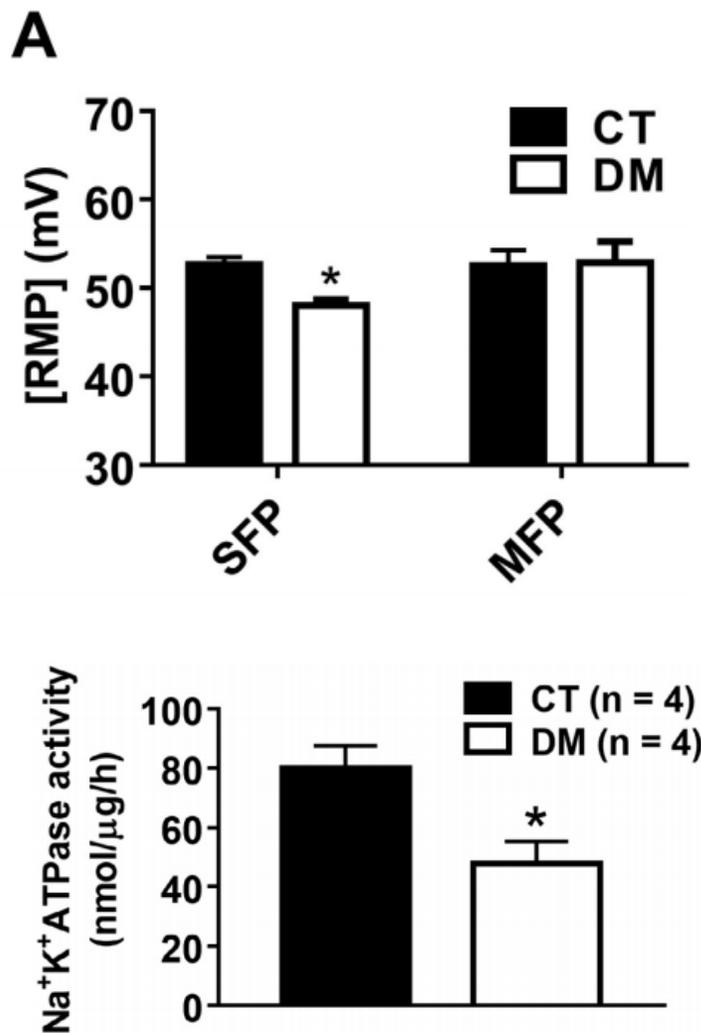
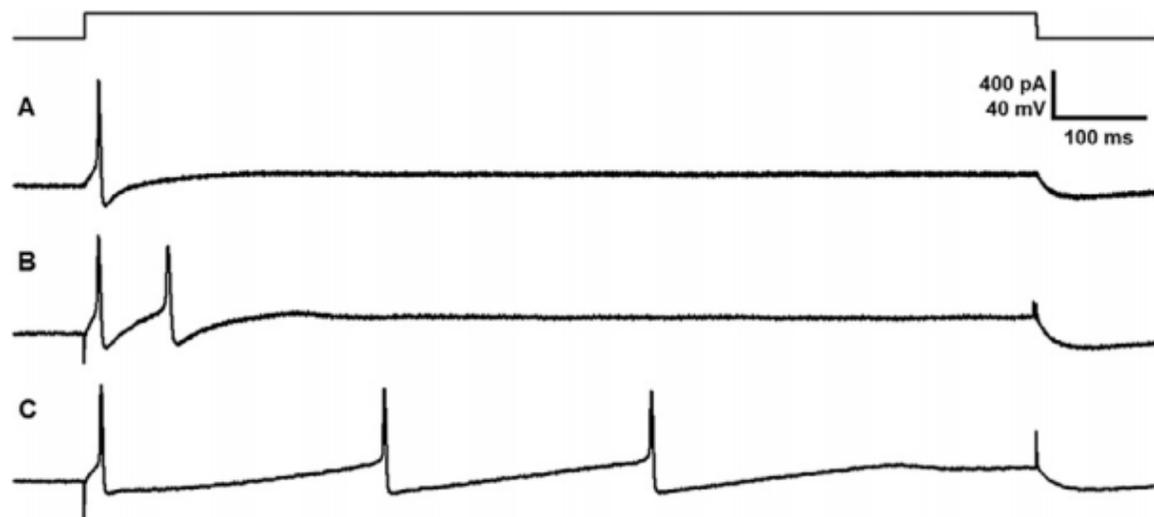


Fig. 4. Effects of diabetes mellitus (DM) on the Na<sup>+</sup> K<sup>+</sup>-ATPase activity of SCC neurons. Activity expressed as mean ± SEM. \*, significant difference compared to control group ( $p < 0.05$ , unpaired Student's *t*-test);  $n = 4$  and  $4$ , for CT and DM groups, respectively.

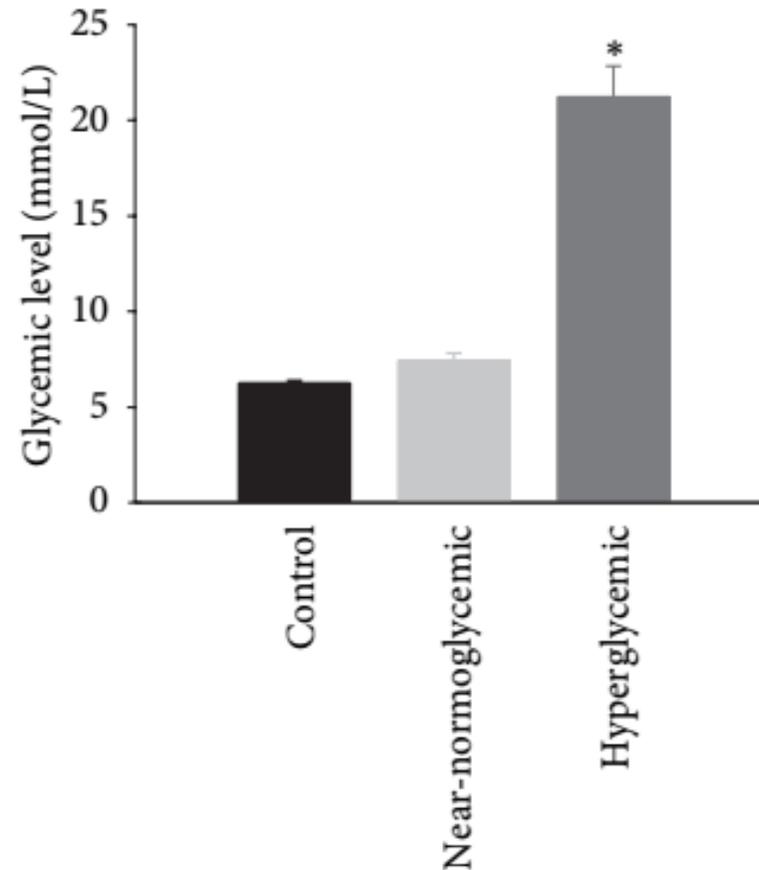
## Em síntese...

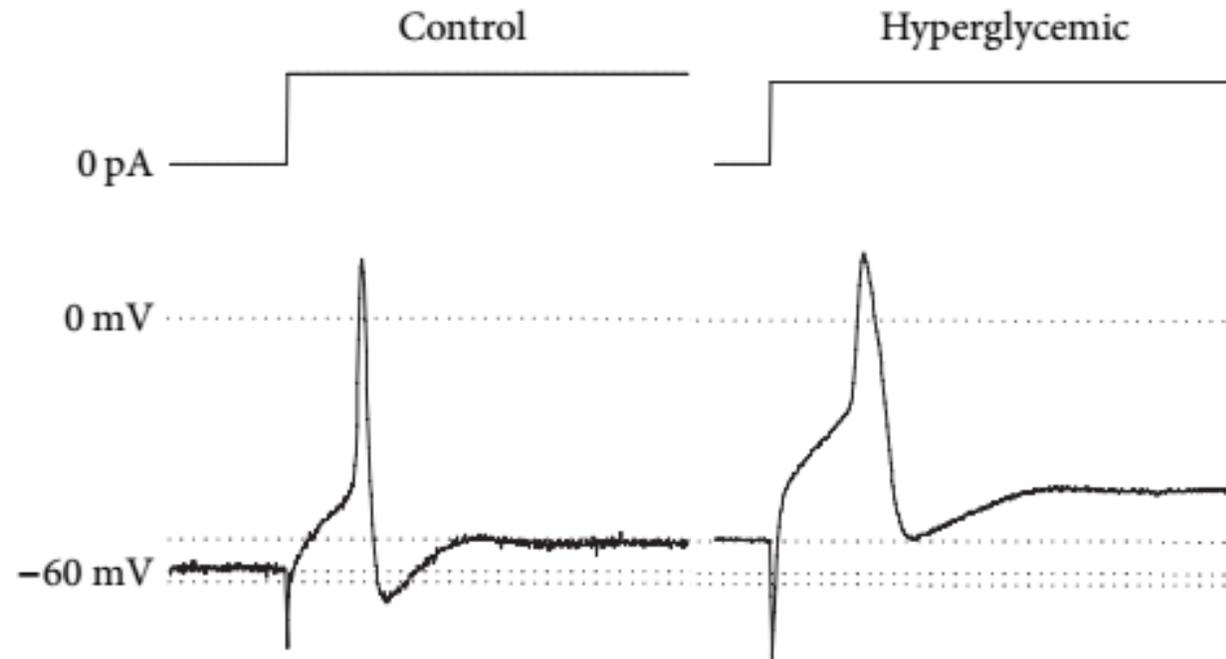
O PR foi despolarizado em neurônios SFP de ratos diabéticos, o tipo mais abundante no GCS de ratos. A diminuição na atividade da  $\text{Na}^+\text{K}^+$ -ATPase é uma hipótese atraente para a explicação dessa alteração.

# n5-STZ Diabetic Model Develops Alterations in Sciatic Nerve and Dorsal Root Ganglia Neurons of Wistar Rats



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Matheus Lemos-dos-Santos,<sup>1</sup> Keciany Alves de Oliveira,<sup>1</sup> Humberto Cavalcante Joca,<sup>1</sup>  
Otoni Cardoso do Vale,<sup>2</sup> Andreлина Noronha Coelho-de-Souza,<sup>1</sup>  
and José Henrique Leal-Cardoso<sup>1</sup>





Parameter	Control	Hyperglycemic
Resting potential (mV)	$-58.3 \pm 1.7$ (11)	$-54.0 \pm 1.4^a$ (11)
Input resistance (M $\Omega$ )	$14.9 \pm 2.2$ (10)	$12.3 \pm 1.5$ (10)
Limiar current (pA)	$1909.1 \pm 315.2$ (11)	$1618.2 \pm 202.2$ (11)
AP amplitude (mV)	$72.7 \pm 3.6$ (11)	$66.1 \pm 3.9$ (11)
AP duration (ms)	$0.9 \pm 0.1$ (11)	$2.0 \pm 0.3^a$ (11)
Maximum ascendant inclination (V/s)	$195.5 \pm 28.9$ (11)	$110.9 \pm 15.3^a$ (11)
Maximum descendant inclination (V/s)	$124.5 \pm 15.0$ (11)	$75.5 \pm 9.2^a$ (11)

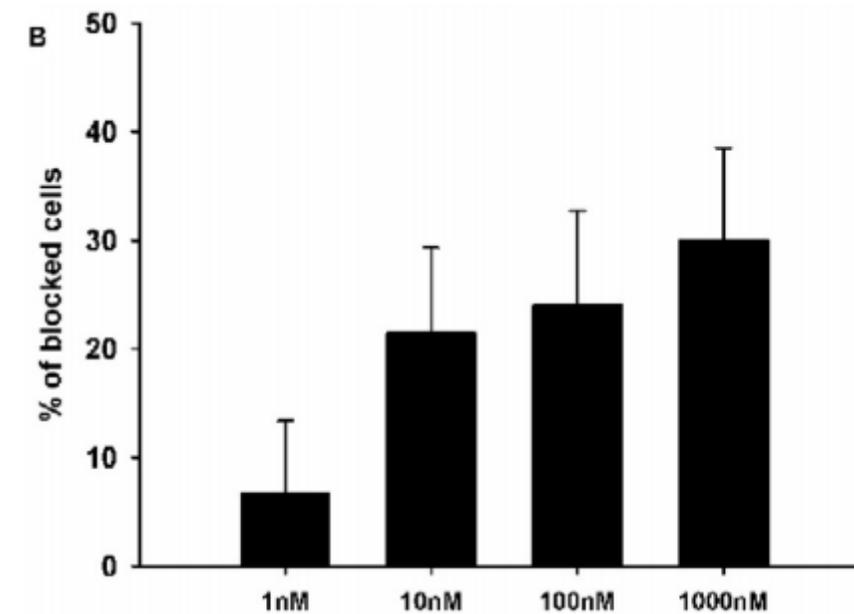
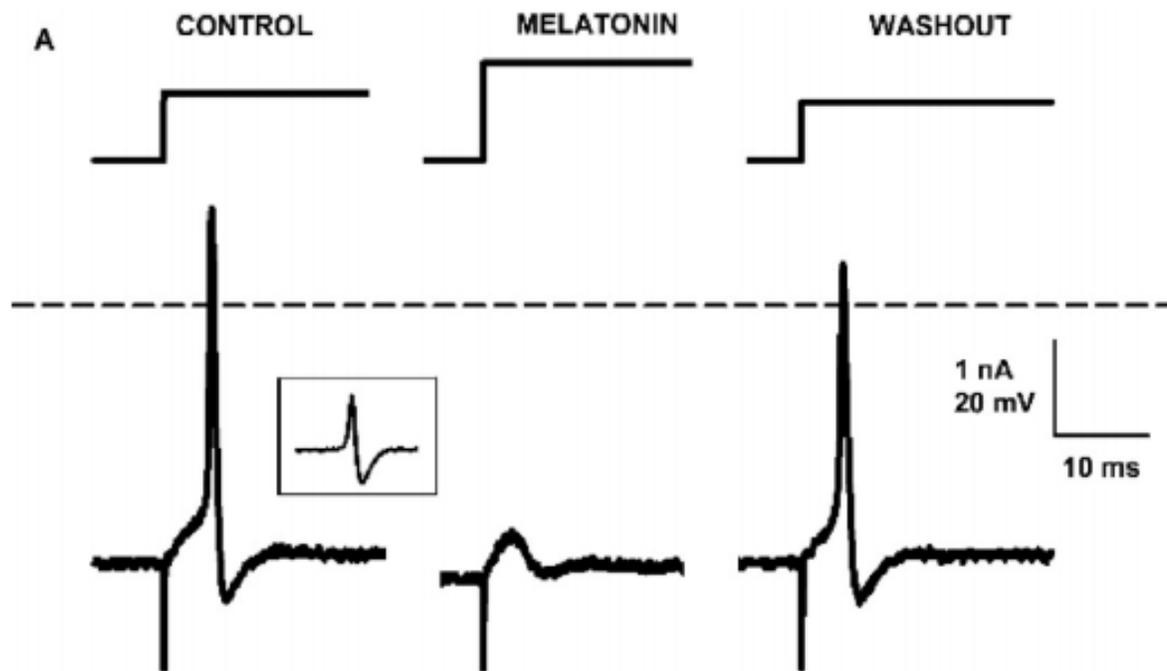
# Melatonin decreases neuronal excitability in a sub-population of dorsal root ganglion neurons

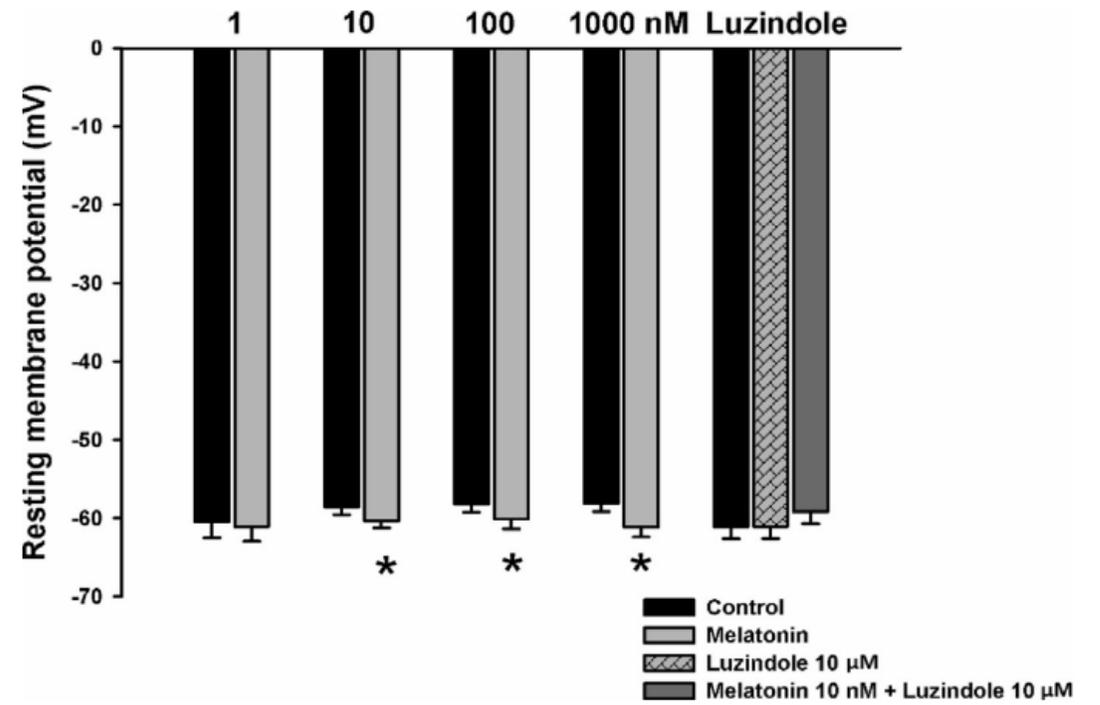
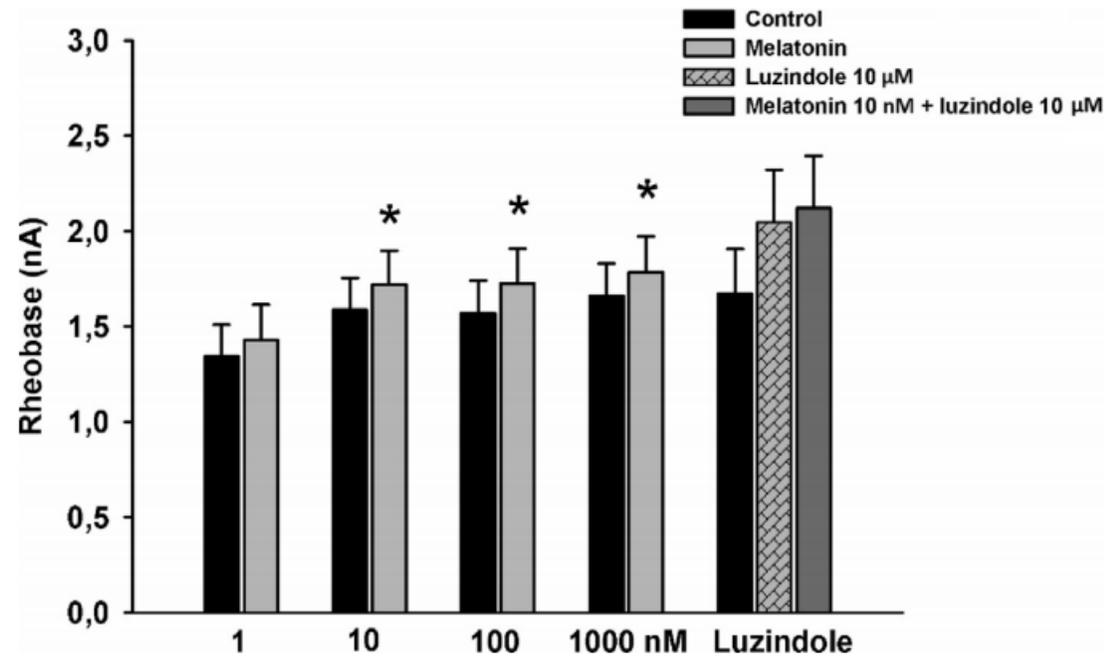


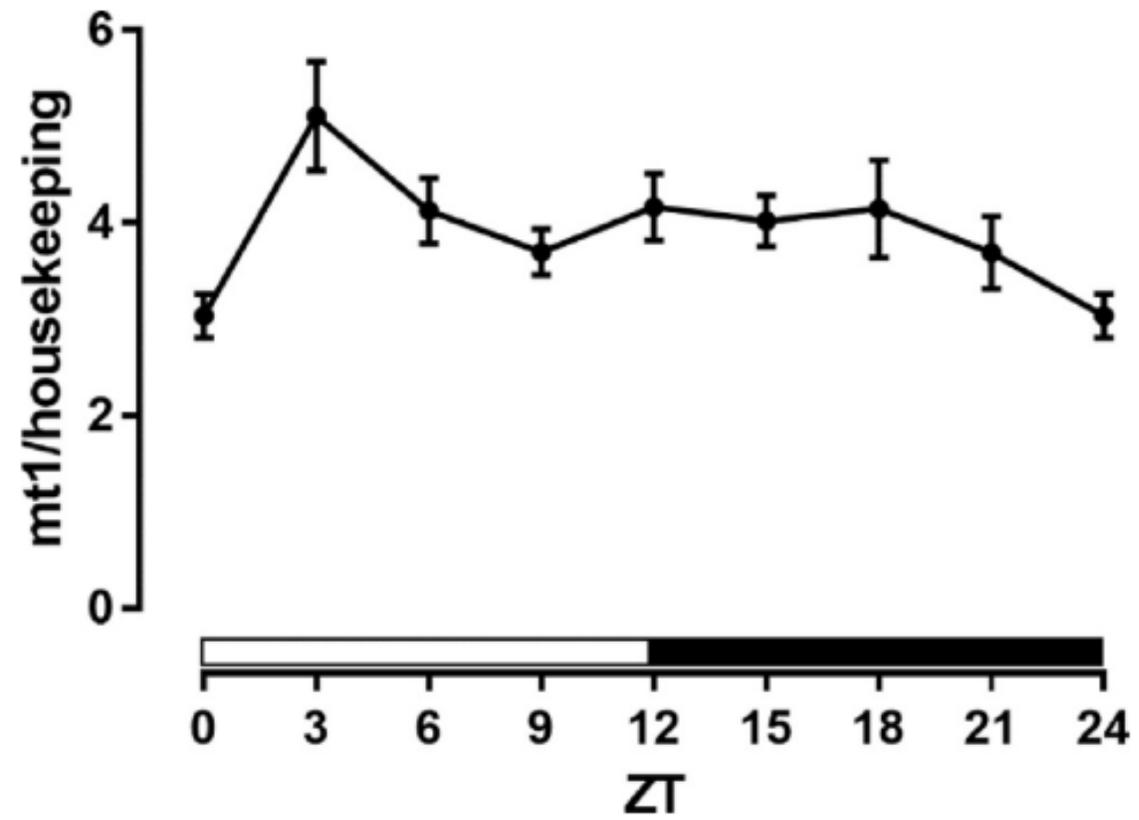
Klausen Oliveira-Abreu<sup>a</sup>, Francisco Walber Ferreira-da-Silva<sup>a</sup>, Kerly Shamyra da Silva-Alves<sup>a</sup>, Nathalia Maria Silva-dos-Santos<sup>a</sup>, Ana Carolina Cardoso-Teixeira<sup>a</sup>, Fernanda Gaspar do Amaral<sup>b</sup>, José Cipolla-Neto<sup>b</sup>, José Henrique Leal-Cardoso<sup>a,\*</sup>

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<sup>b</sup>Laboratório de Neurobiologia, Instituto de Ciências Biomédicas 1, Universidade de São Paulo, São Paulo, SP, Brazil







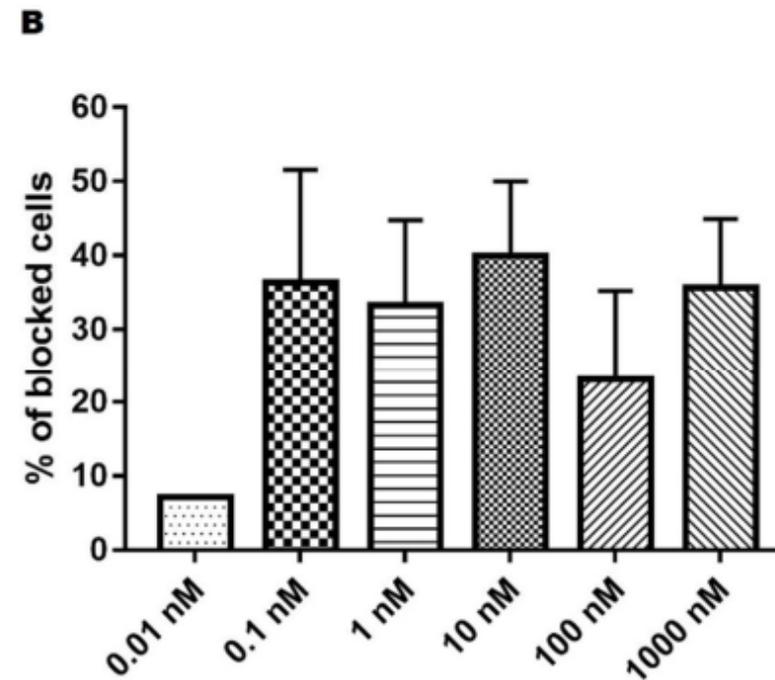
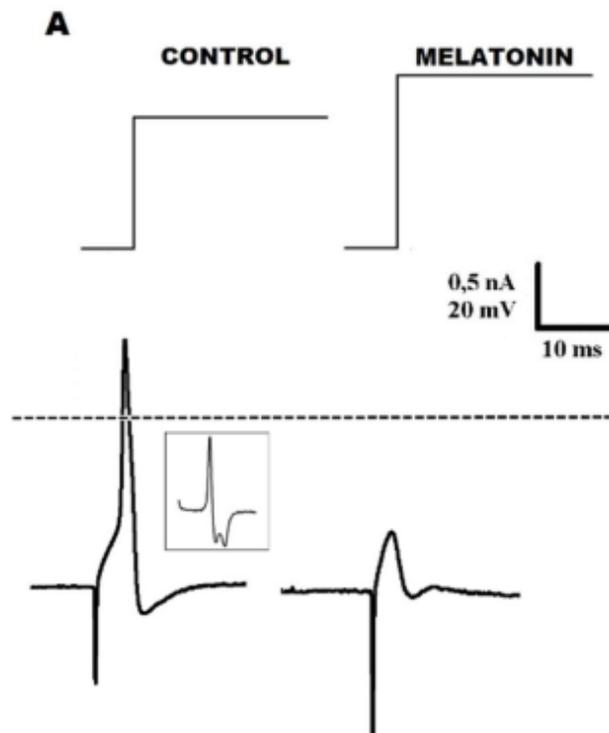
## Em síntese...

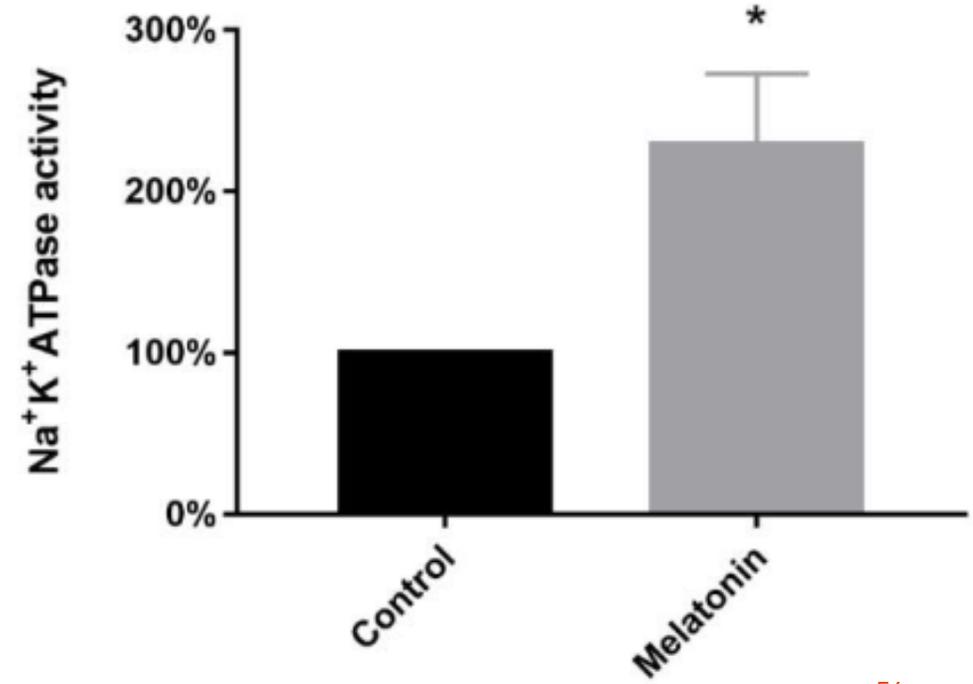
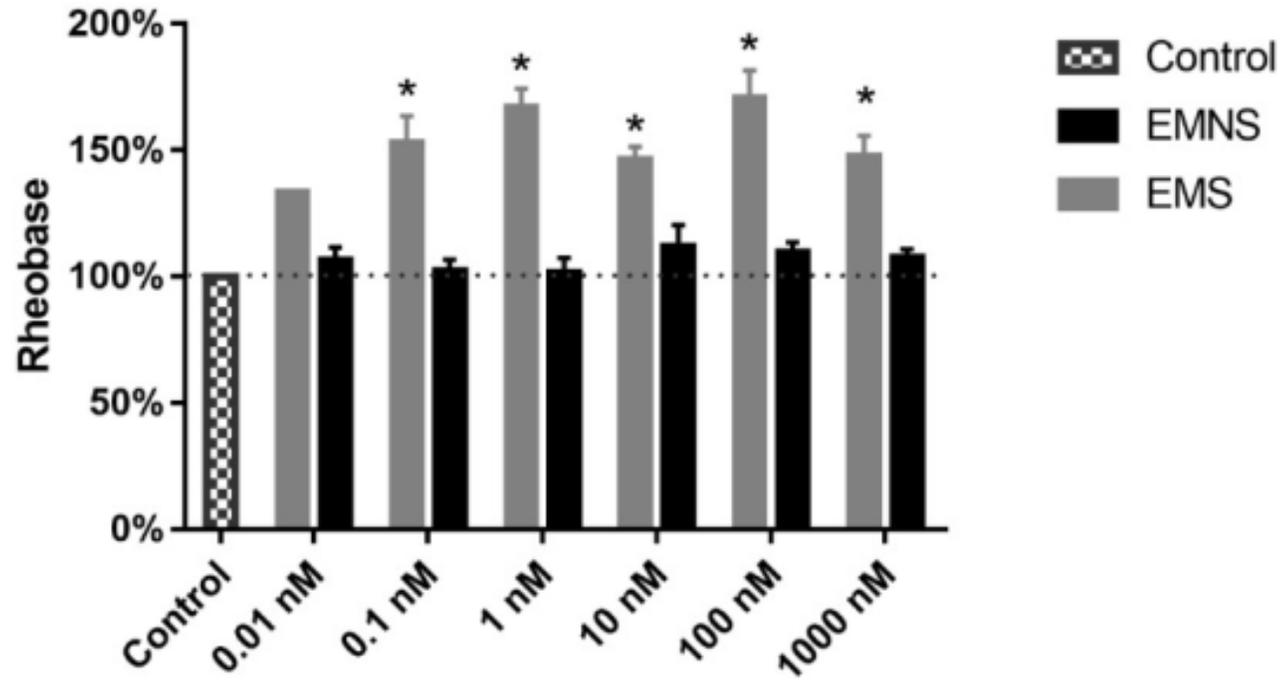
A melatonina reduz a excitabilidade em neurônios  $N_0$ . A concentração mínima efetiva (10 nM) e o bloqueio dos efeitos da melatonina pelo luzindol sugerem que o efeito da melatonina é hormonal e é induzido por meio da sua ligação aos receptores  $MT_1$ .

Article

# Melatonin Reduces Excitability in Dorsal Root Ganglia Neurons with Inflection on the Repolarization Phase of the Action Potential

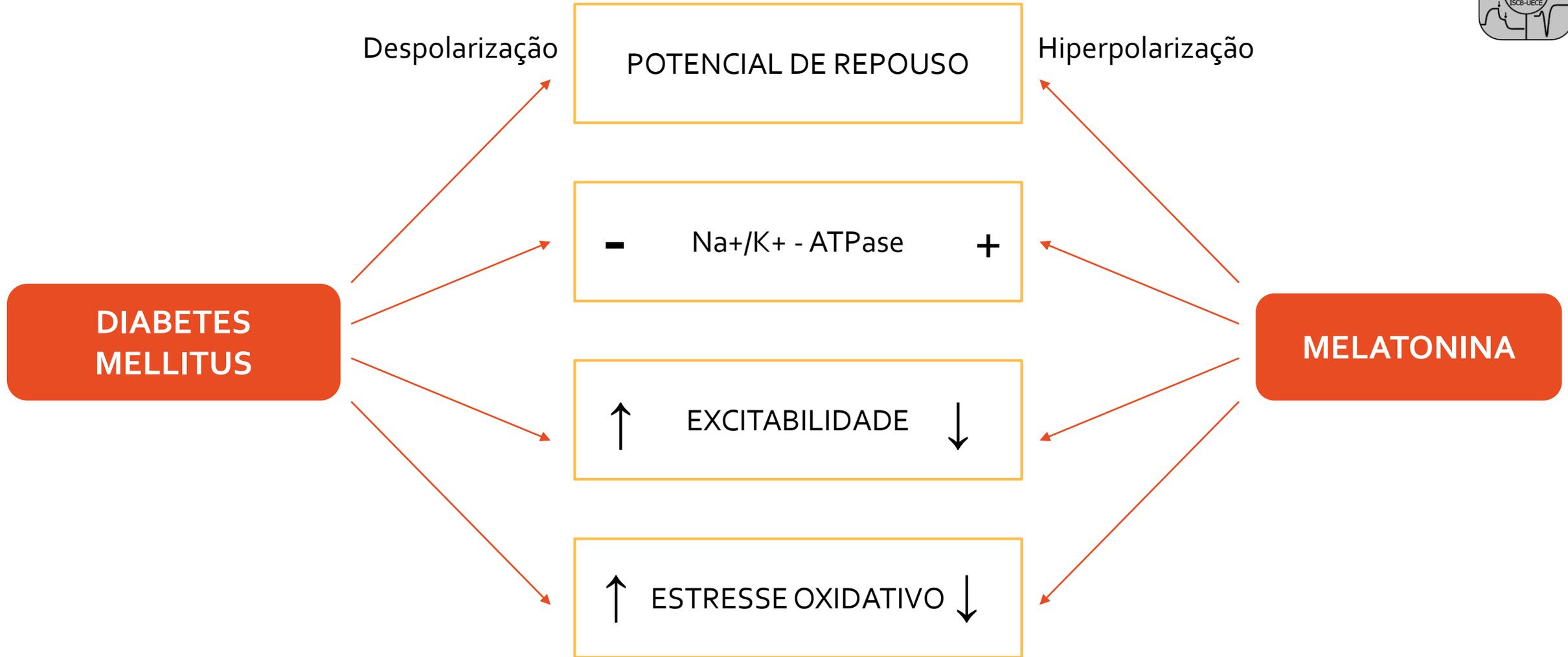
Klausen Oliveira-Abreu <sup>1</sup>, Nathalia Maria Silva-dos-Santos <sup>1</sup>,  
 Andrelina Noronha Coelho-de-Souza <sup>1</sup>, Francisco Walber Ferreira-da-Silva <sup>1</sup>,  
 Kerly Shamyra da Silva-Alves <sup>1</sup>, Ana Carolina Cardoso-Teixeira <sup>1</sup>, José Cipolla-Neto <sup>2</sup> and  
 José Henrique Leal-Cardoso <sup>1,\*</sup>

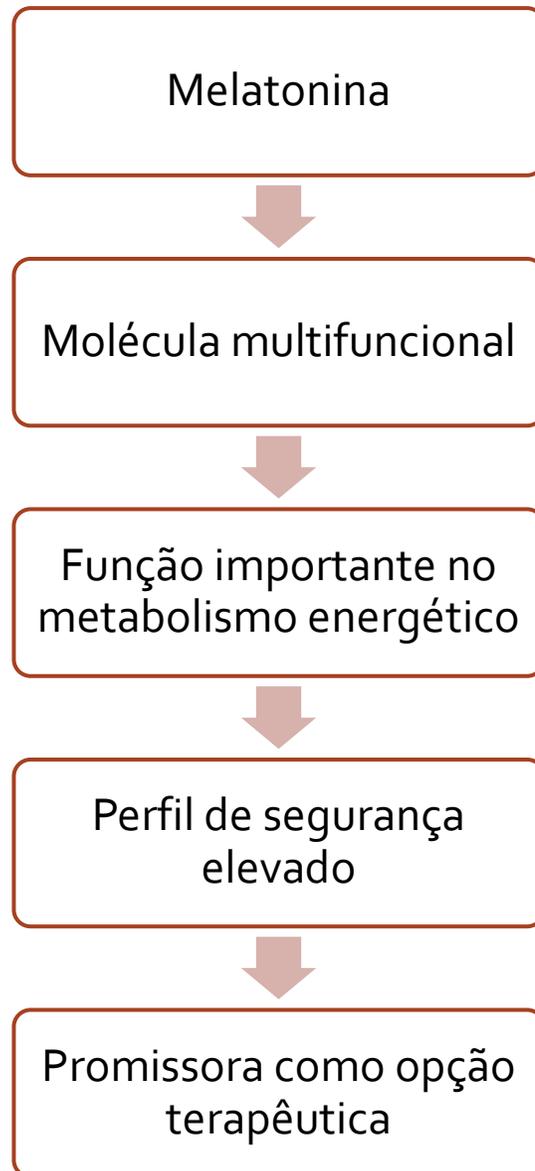




## Em síntese...

A melatonina reduz a excitabilidade de algumas células  $N_{inf}$  com uma grande potência farmacológica e estimula a atividade da  $Na^+K^+$ -ATPase. Em conjunto, sugere-se que a melatonina atua no GRD na modulação de um tipo específico de sensação de dor, podendo assim se tornar um agente terapêutico importante.





# Conclusão



**OBRI5GADO PELA ATENÇÃO!**

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