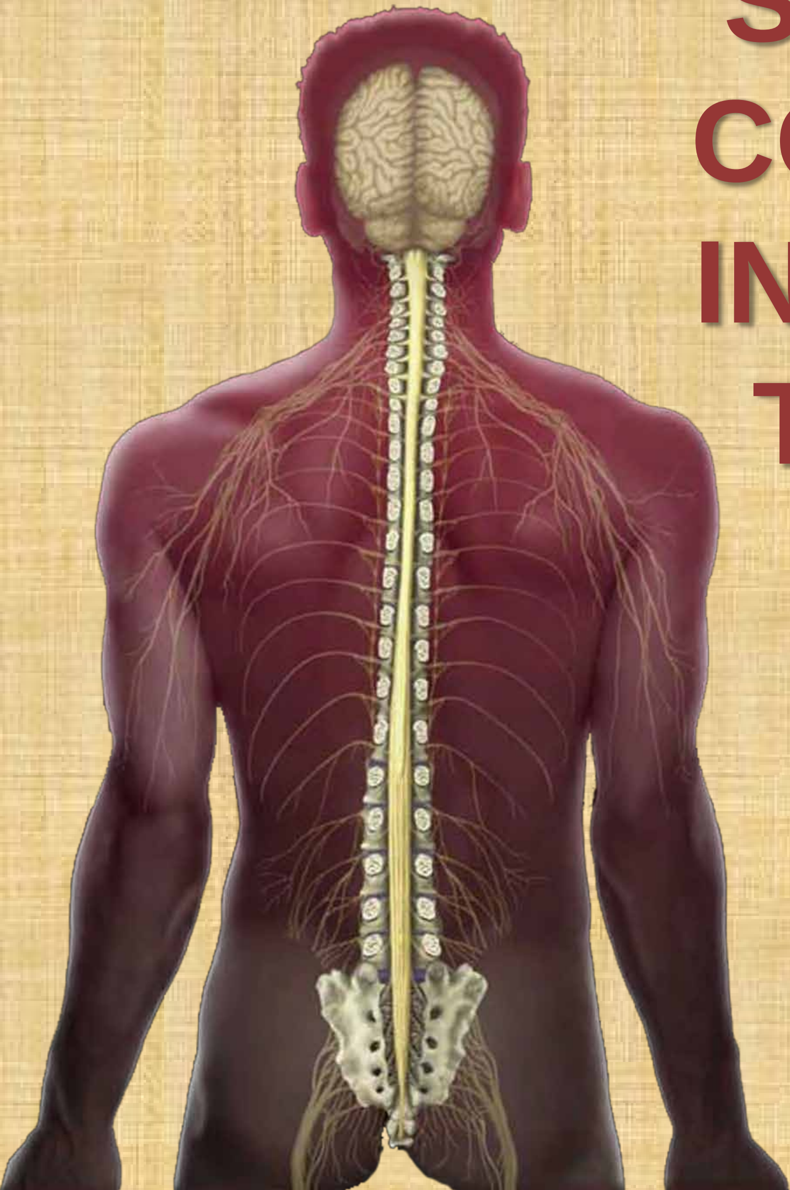


CENTRAL NERVOUS SYSTEM AND THE CONTRIBUTION OF INFLAMMATION TO TISSUE DAMAGE AFTER INJURY

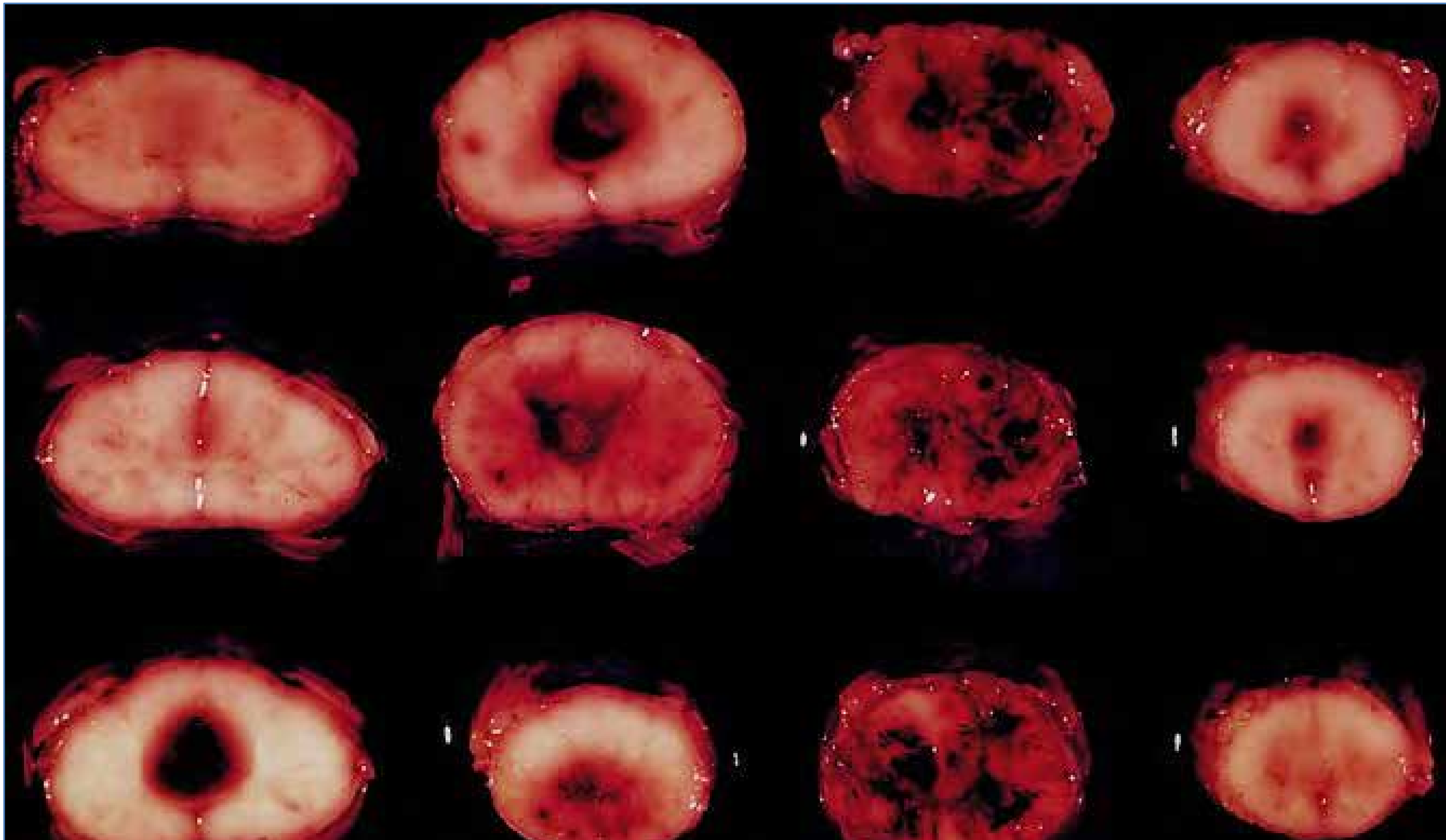
Rubèn López-Vales PhD

Institut de Neurociències

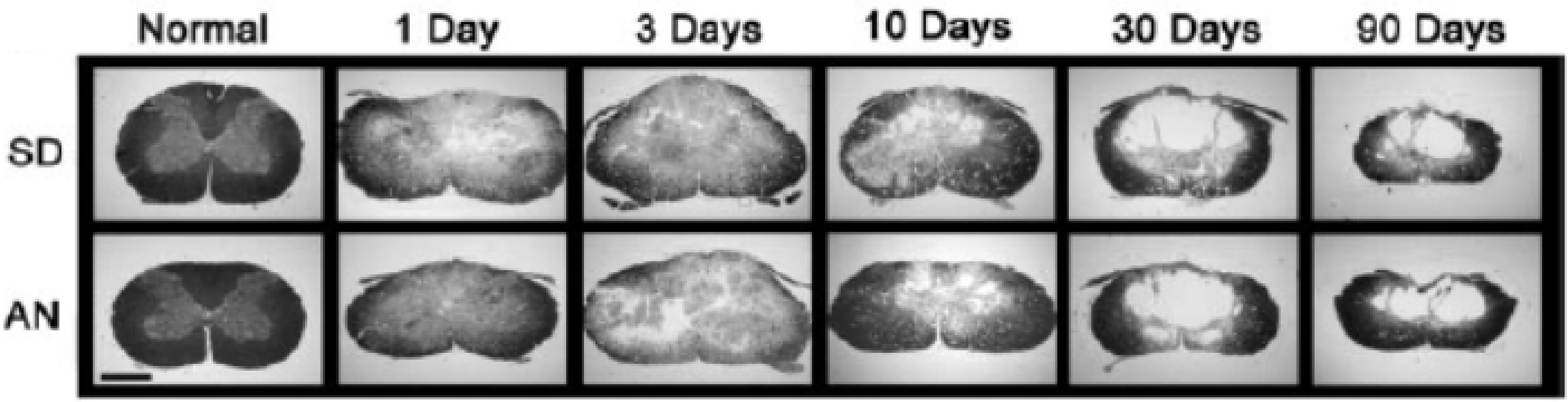
Department of Cell Biology, Physiology and Immunology

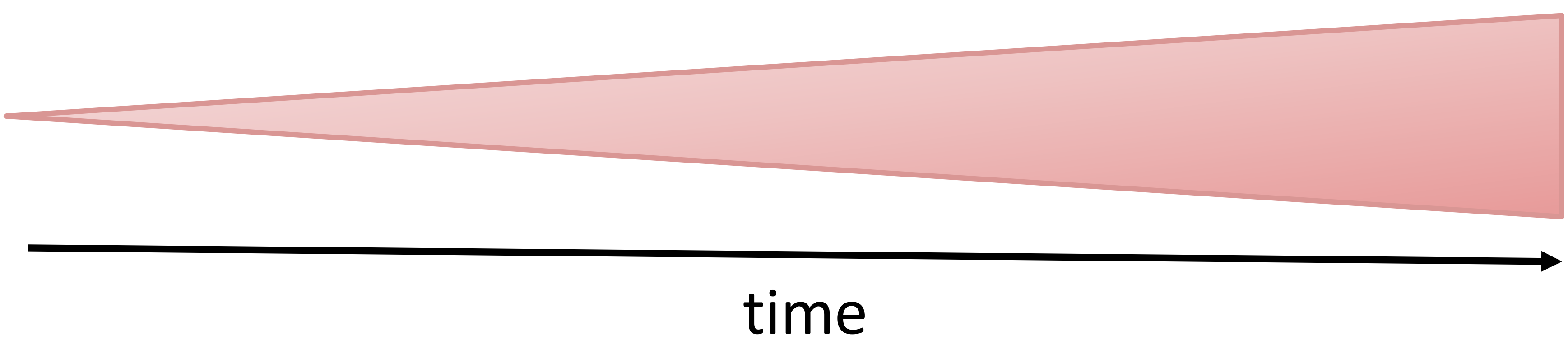
Universitat Autònoma de Barcelona

Spinal cord injury: tissue degeneration

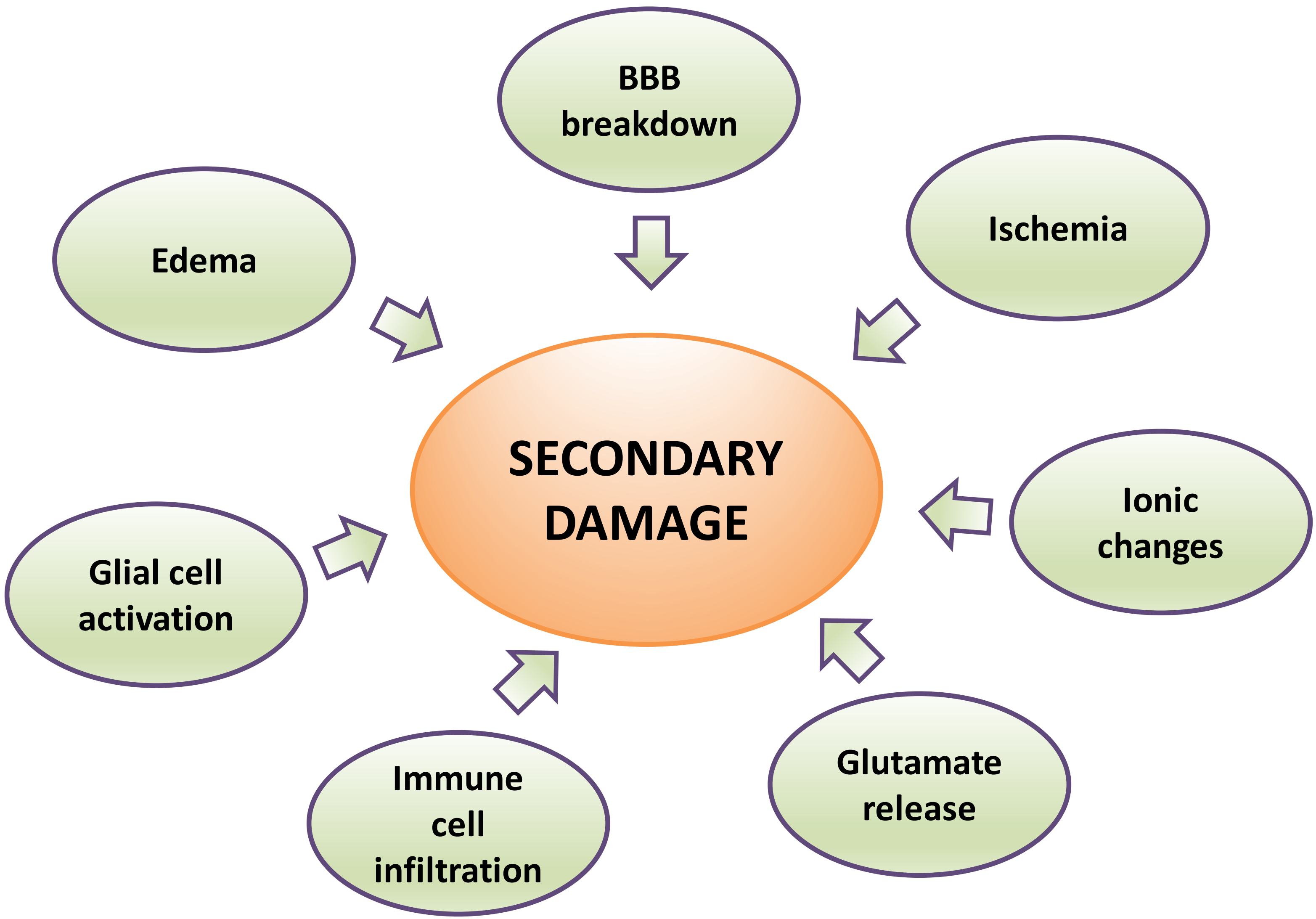


Spinal cord injury: secondary degeneration

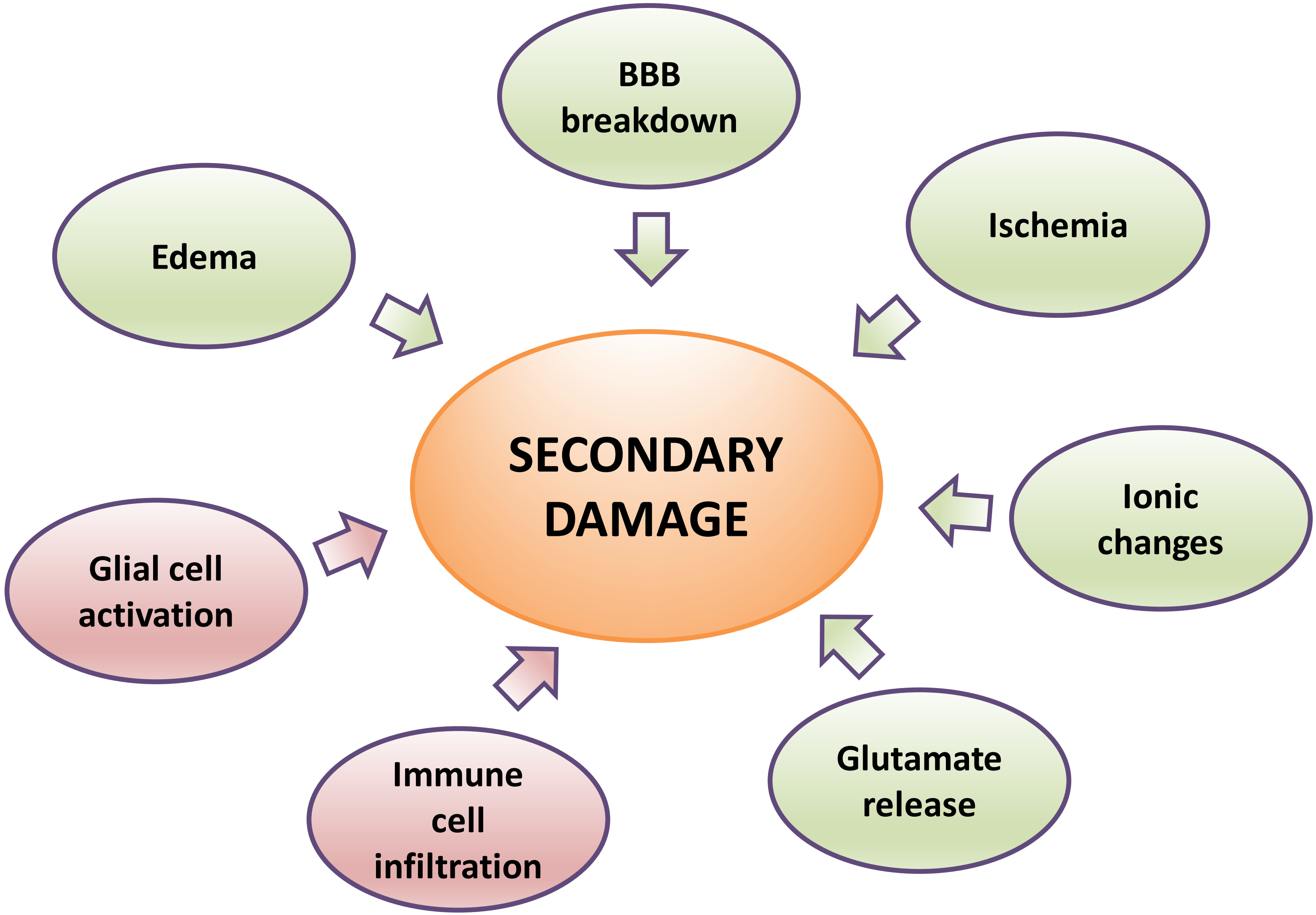


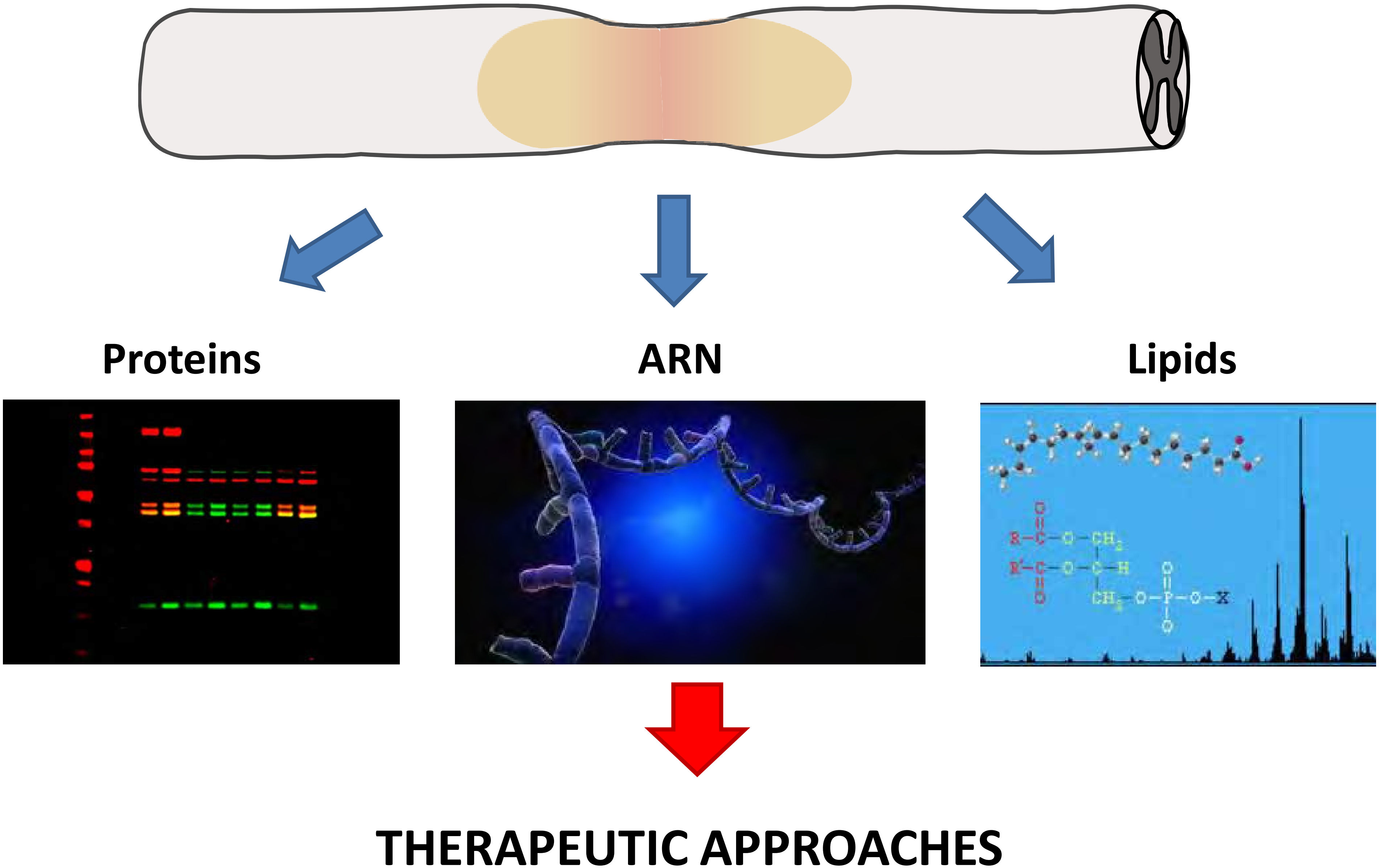


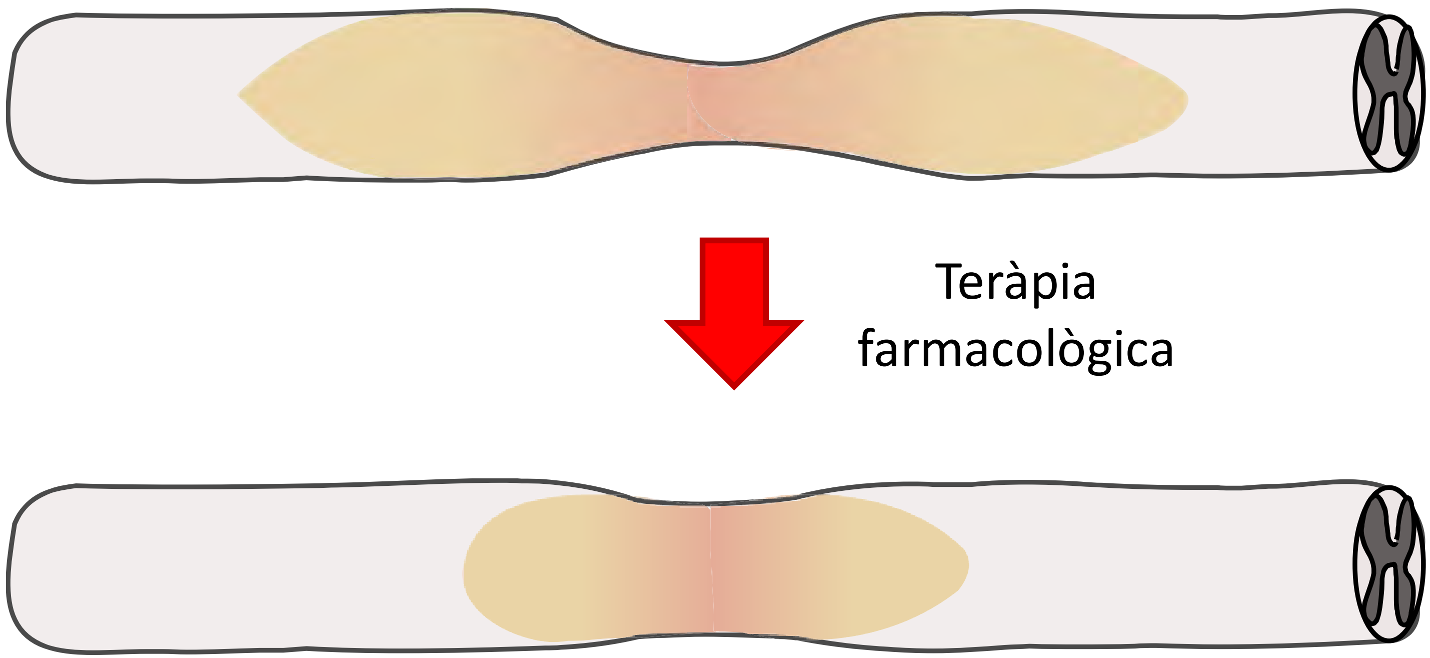
Spinal cord injury: secondary degeneration



Spinal cord injury: secondary degeneration

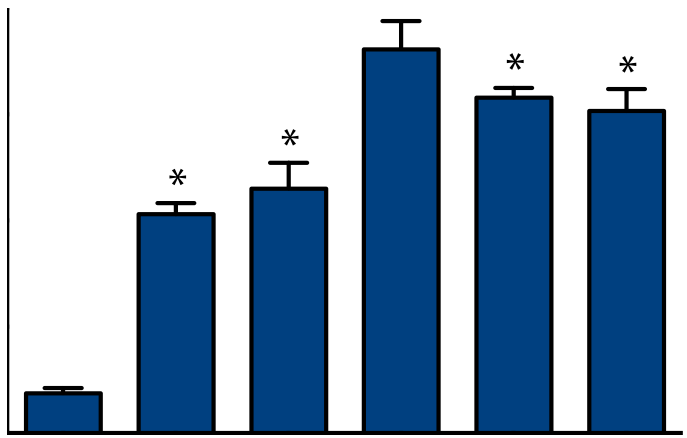



Proteins
ARN
Lipids
THERAPEUTIC APPROACHES


Teràpia
farmacològica

Lysophosphatidic Acid

LPA levels increase in the spinal cord tissue after injury.

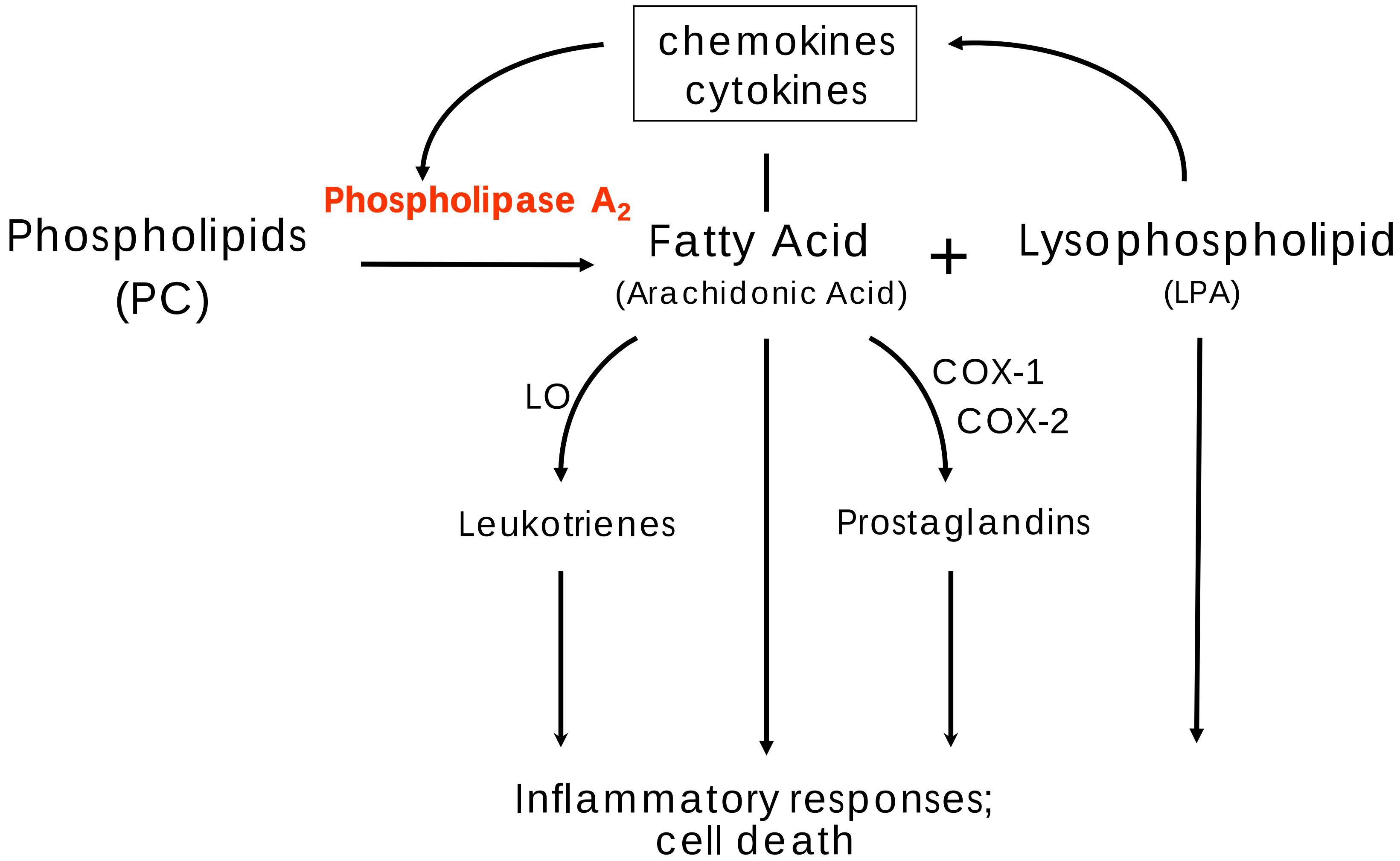


* p < 0,05 vs. naïve

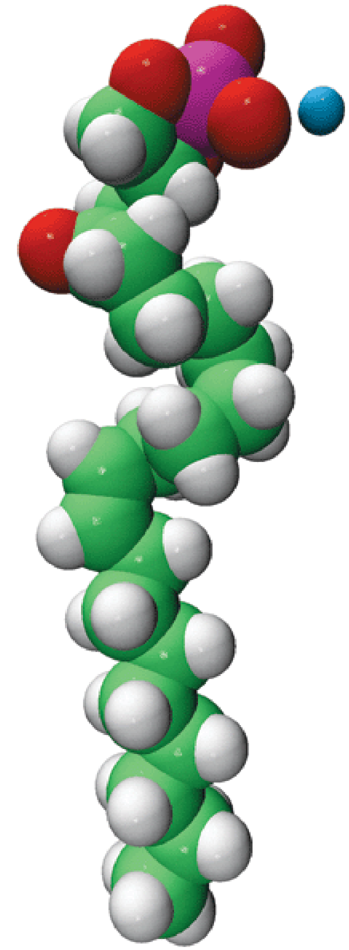
	16:0	18:1	18:0	20:4	20:1	22:6	22:4	22:1
Naïve SC	✗	✓	✓	✗	✓	✗	✗	✗
Injured SC	✓	✓	✓	✓	✓	✓	✓	✓

Santos-Nogueira et al., 2015 J Neurosci

Lysophosphatidic Acid



Lysophosphatidic Acid



LPA has wide variety of biological functions:

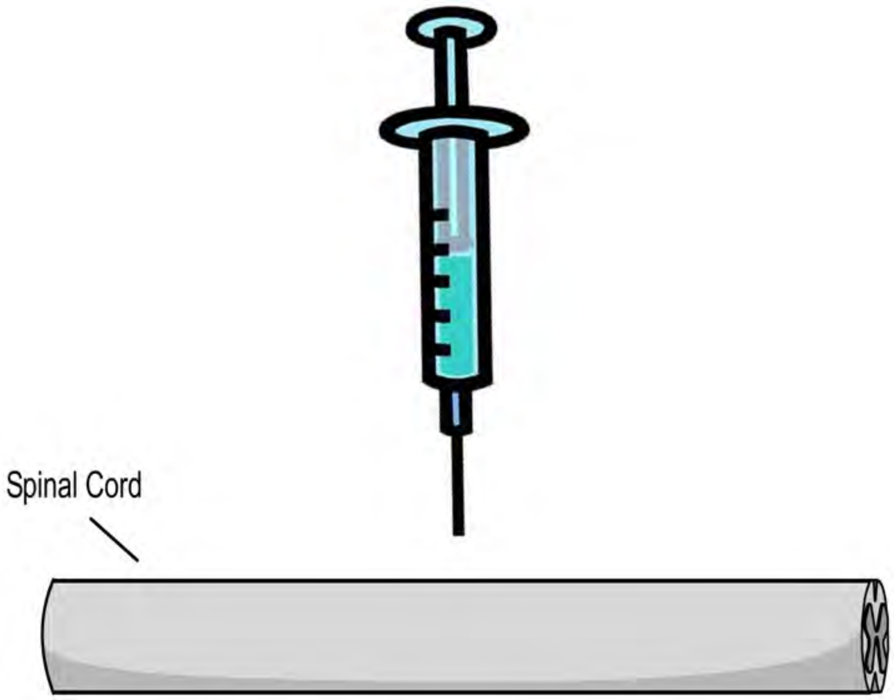
- Stimulation of cell proliferation
- Prevention of apoptosis
- Cell migration
- Inflammation
- Platelet aggregation, etc..

Atherosclerosis, cancer and pulmonary fibrosis.

In vitro studies: neurite retraction, neuronal death and microglial activation.

Lysophosphatidic Acid

LPA INTRASPINAL INJECTION

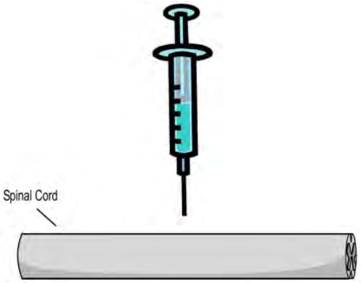


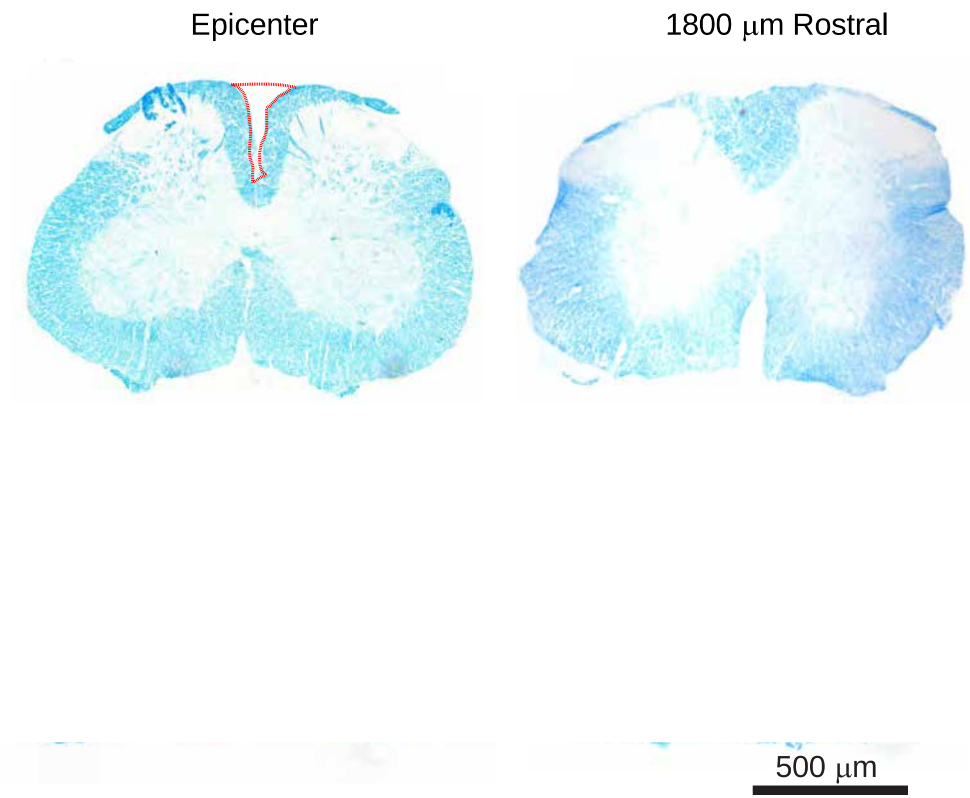
Strain: C57Bl/6

Level: T11

Volume: 1μl containing 5nmoles of LPA

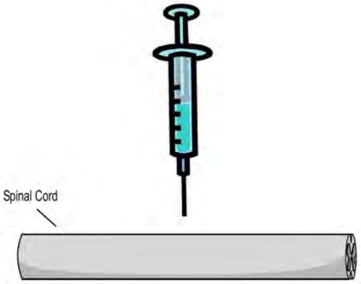
Lysophosphatidic Acid

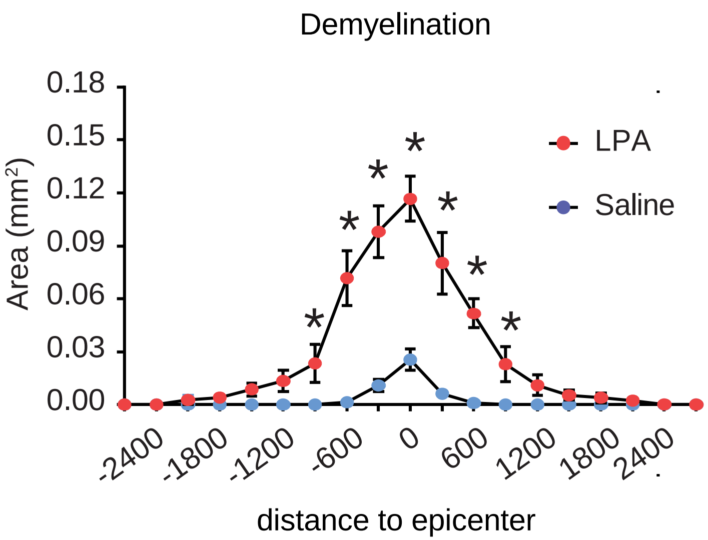


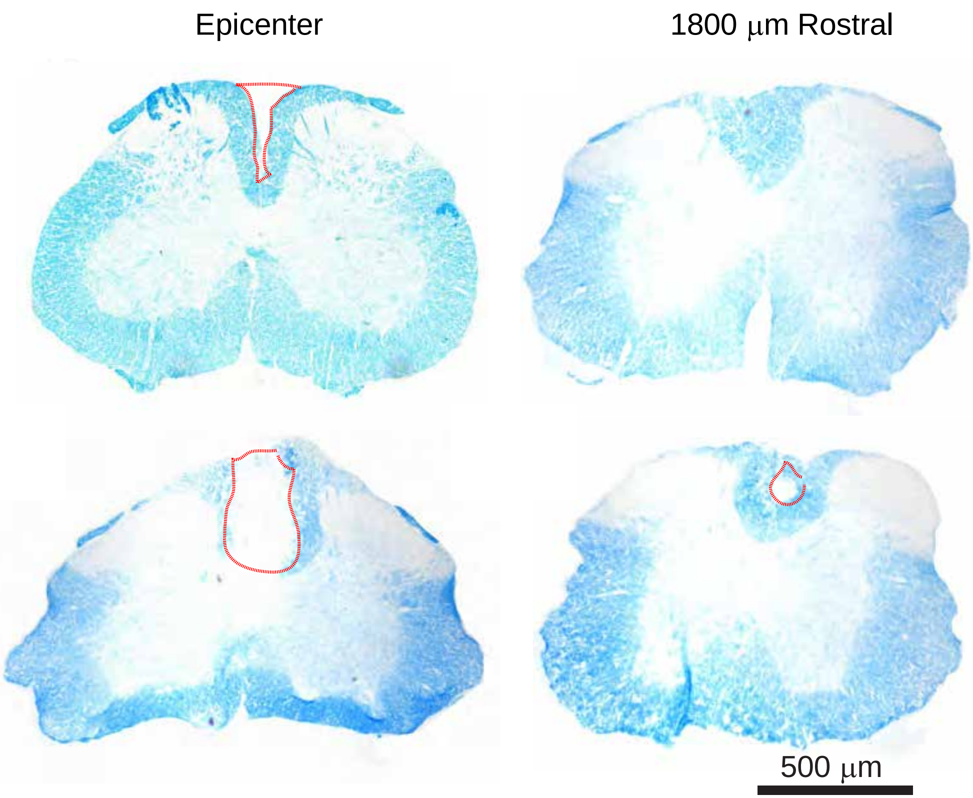


Santos-Nogueira et al., 2015 J Neurosci

Lysophosphatidic Acid

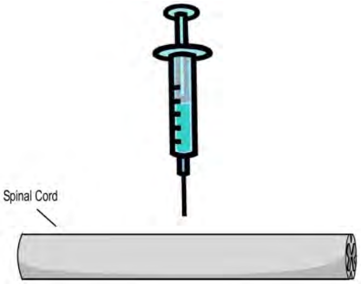


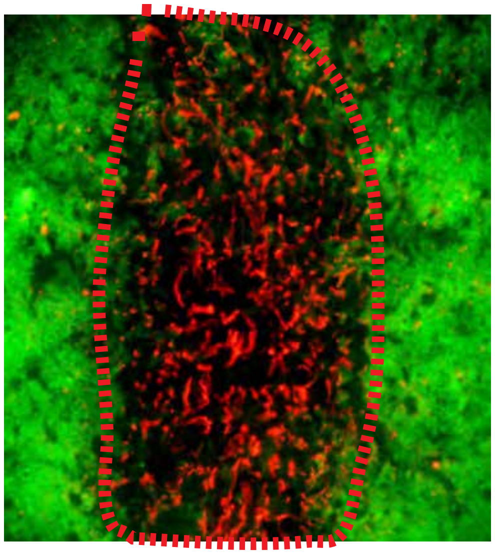




Santos-Nogueira et al., 2015 J Neurosci

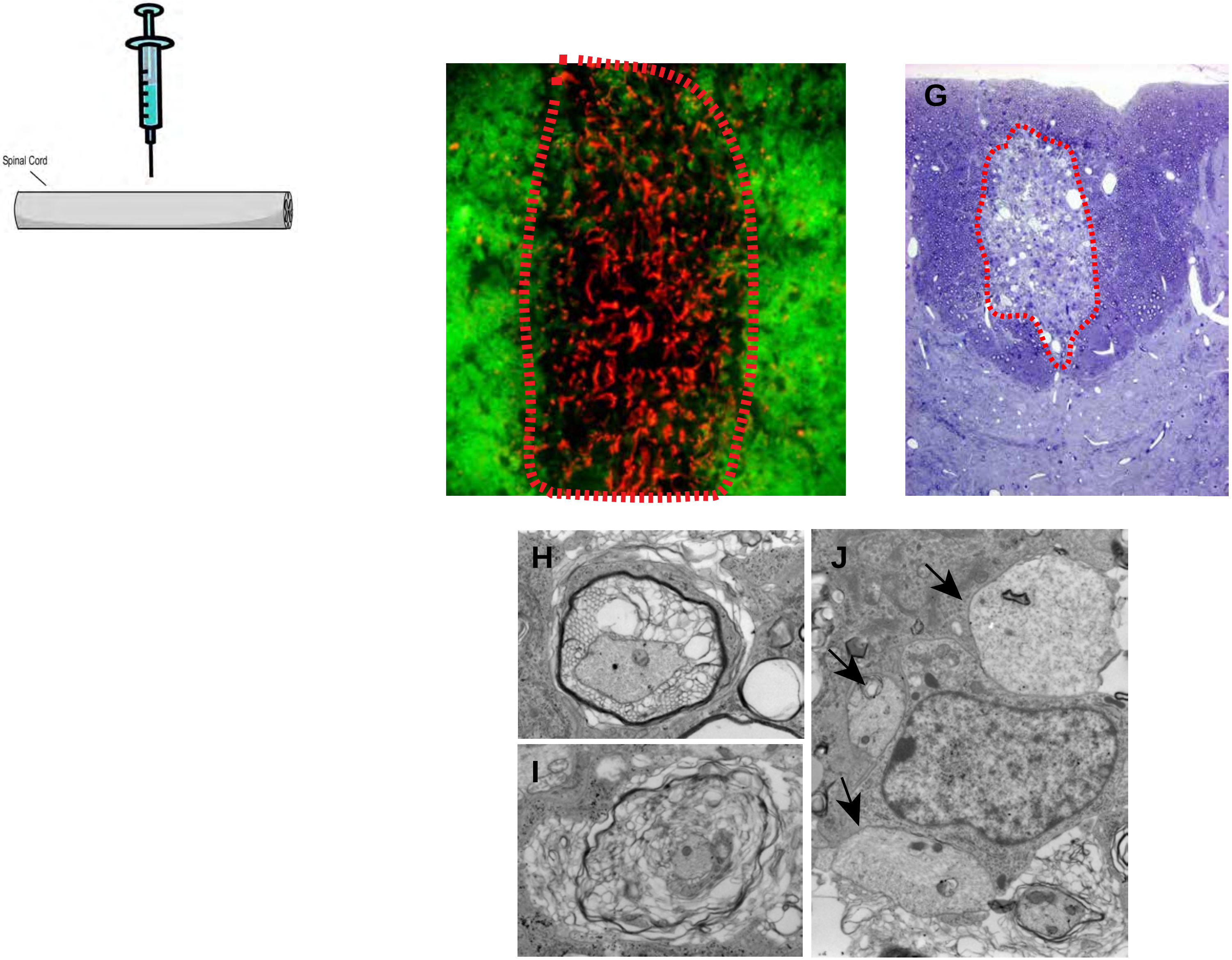
Lysophosphatidic Acid





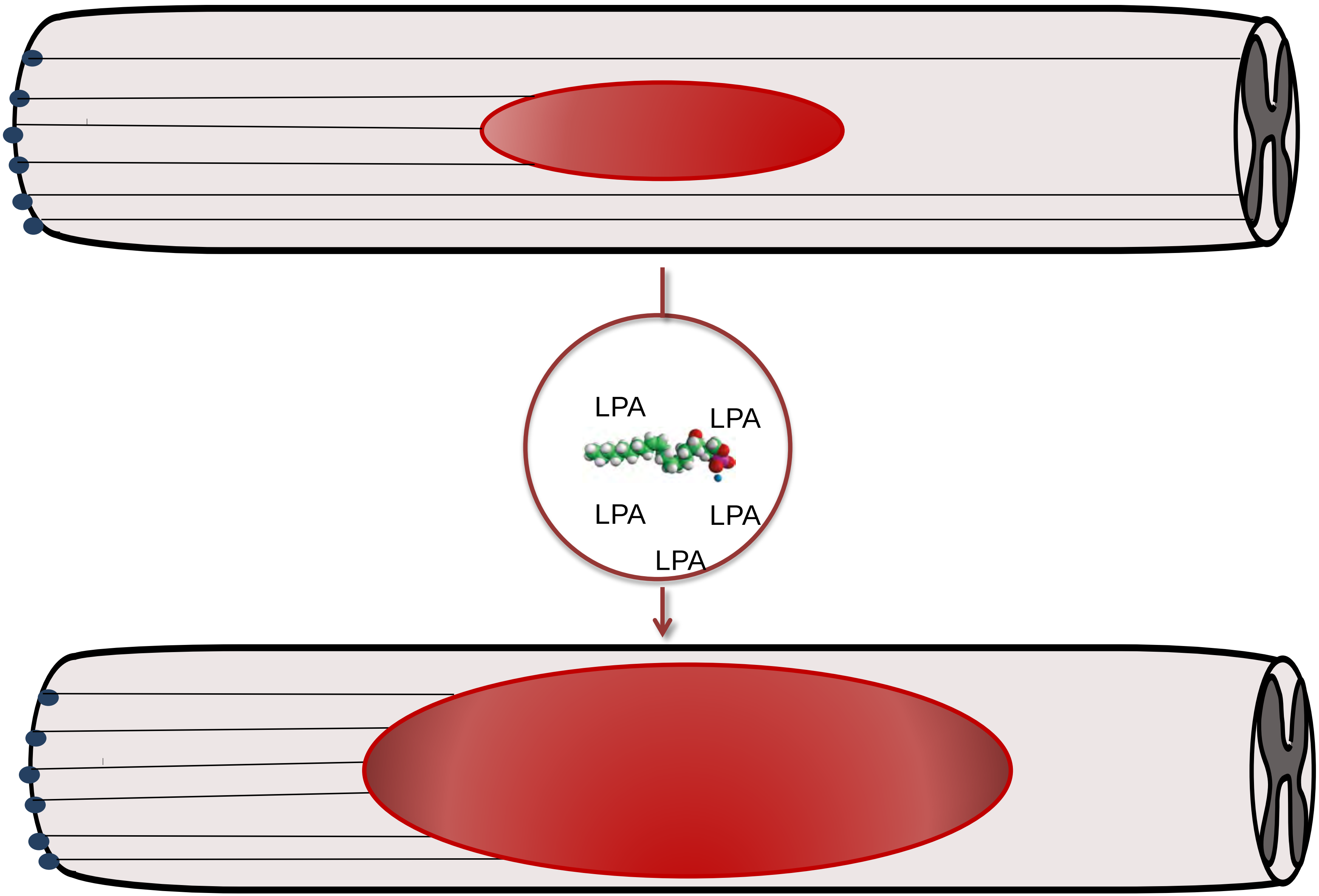
Santos-Nogueira et al., 2015 J Neurosci

Lysophosphatidic Acid

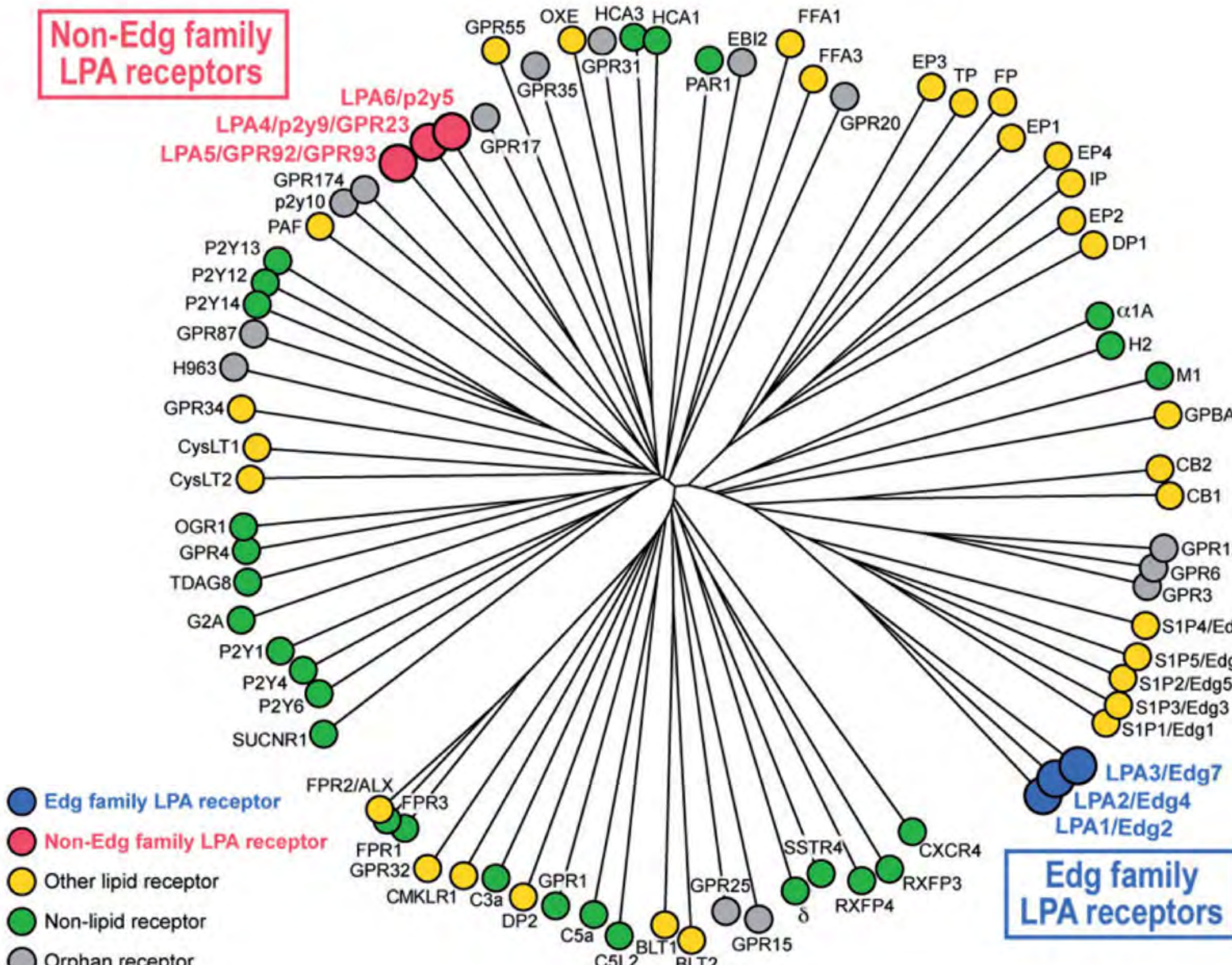


Santos-Nogueira et al., 2015 J Neurosci

Lysophosphatydic Acid

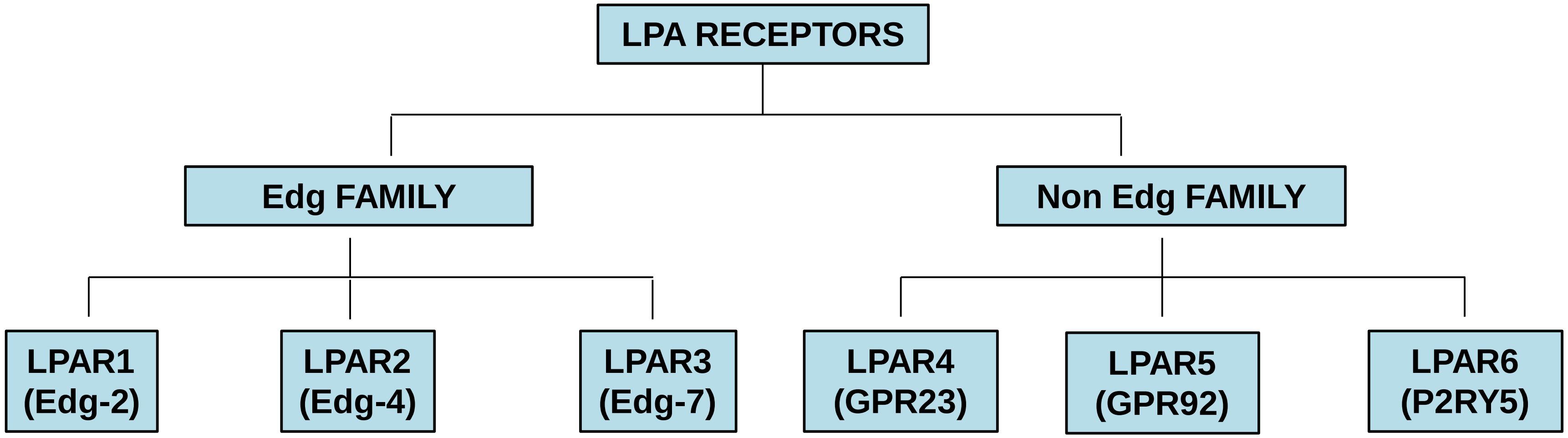


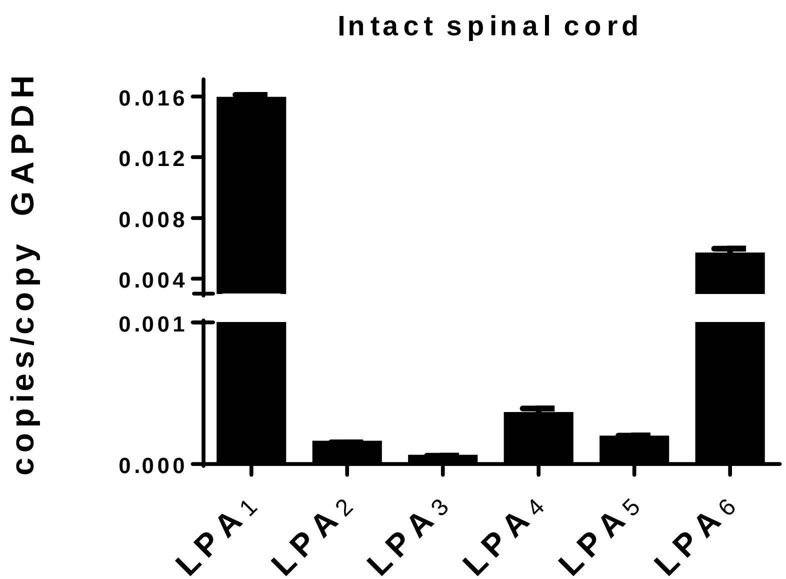
Lysophosphatidic Acid



Yamagida and Ishii, 2011, J Biochem

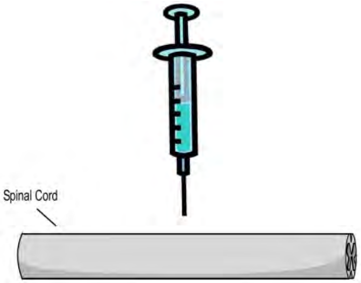
Lysophosphatydic Acid



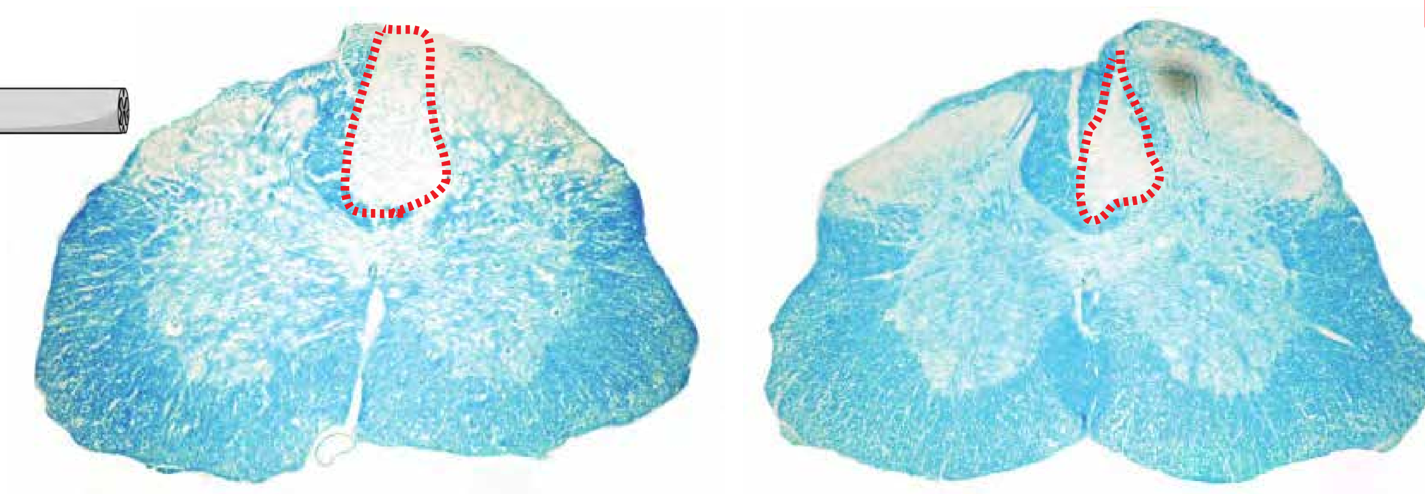


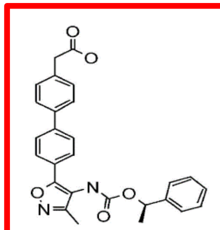
Santos-Nogueira et al., 2015 J Neurosci

LPA receptor 1

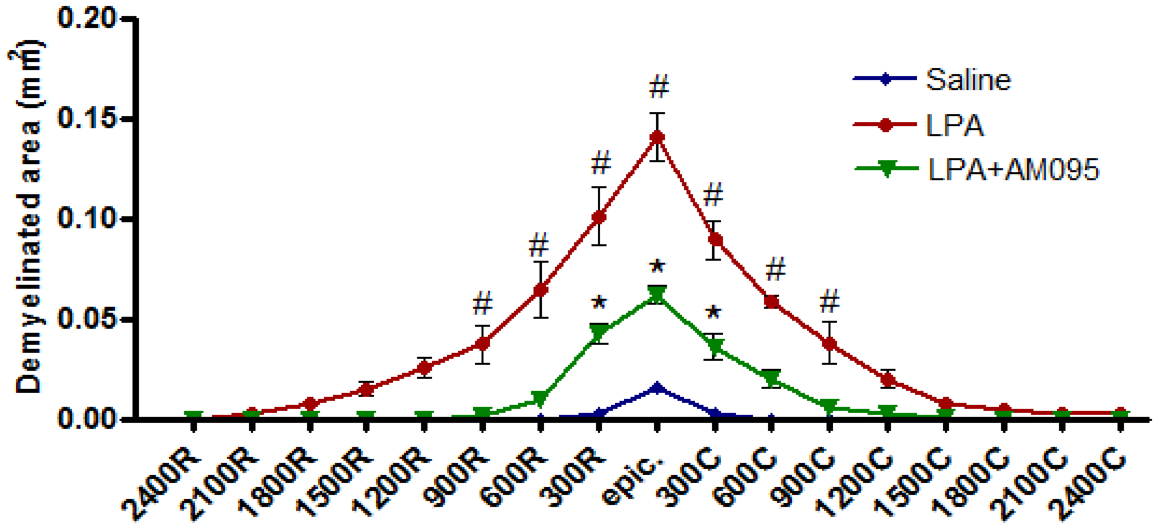


LPA | LPA + AM095





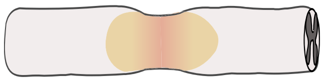
AM095

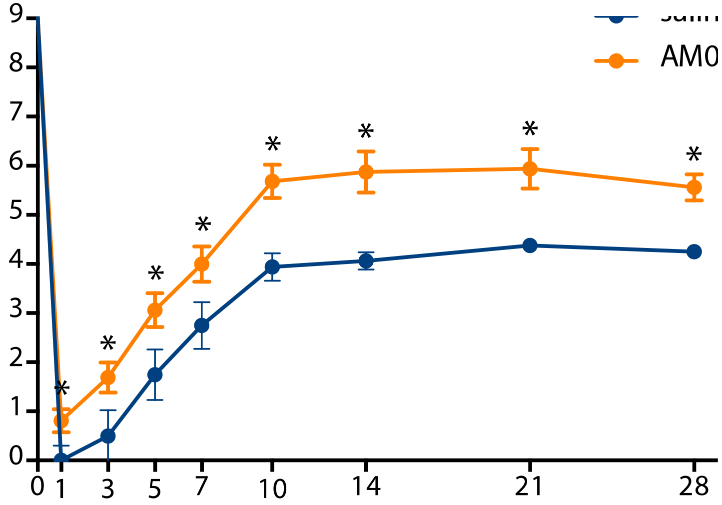


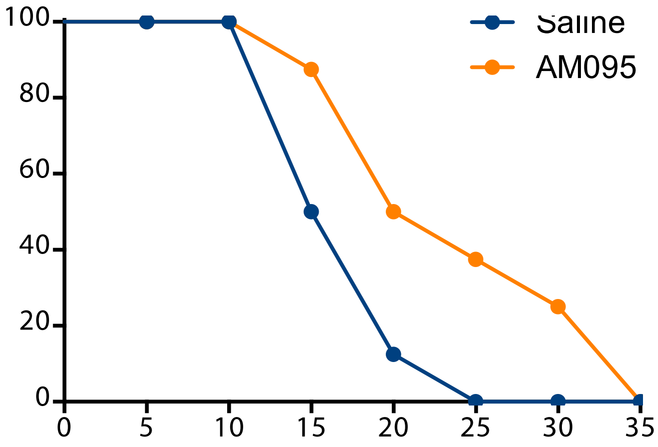
# $p < 0.05$ LPA *vs.* saline
* $P < 0.05$ AM095 *vs.* LPA

Santos-Nogueira et al., 2015 J Neurosci

LPA receptor 1



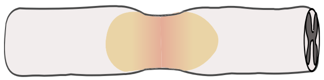


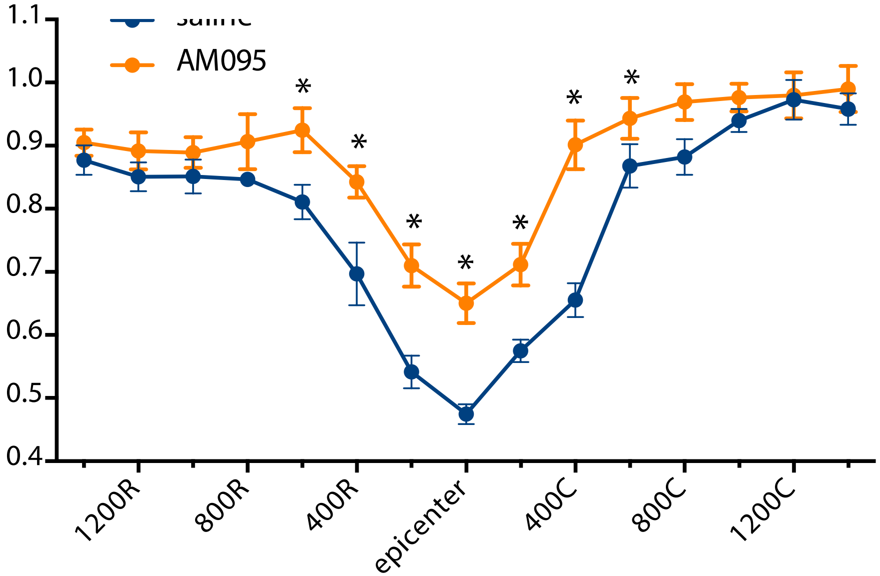


* $p < 0.05$

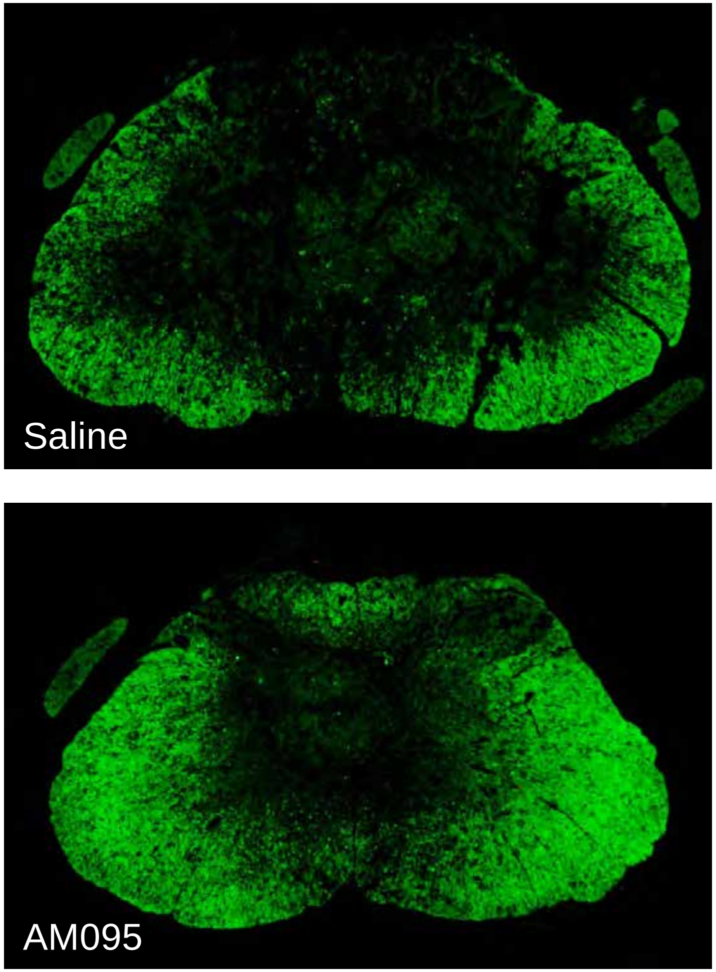
Santos-Nogueira et al., 2015 J Neurosci

LPA receptor 1





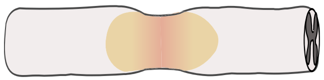
Epicenter

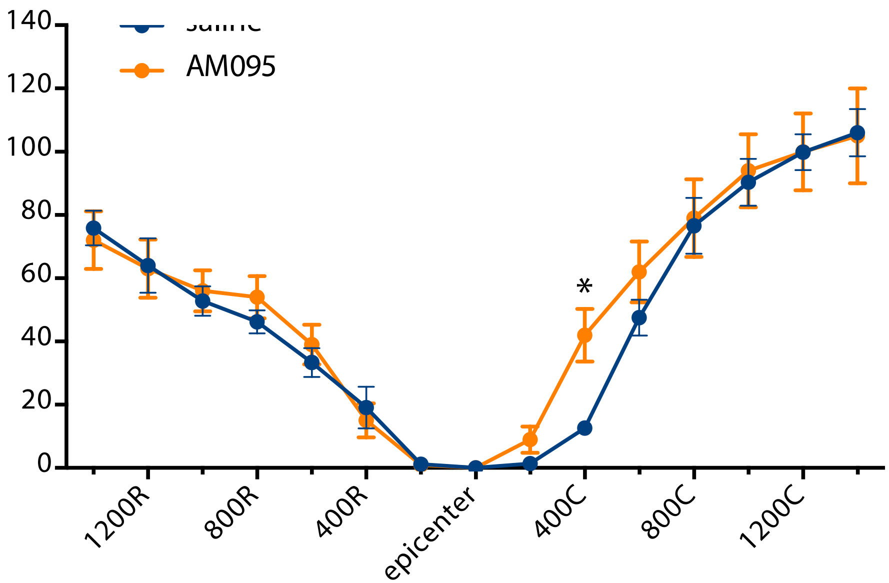


$* \ p < 0.05$

Santos-Nogueira et al., 2015 J Neurosci

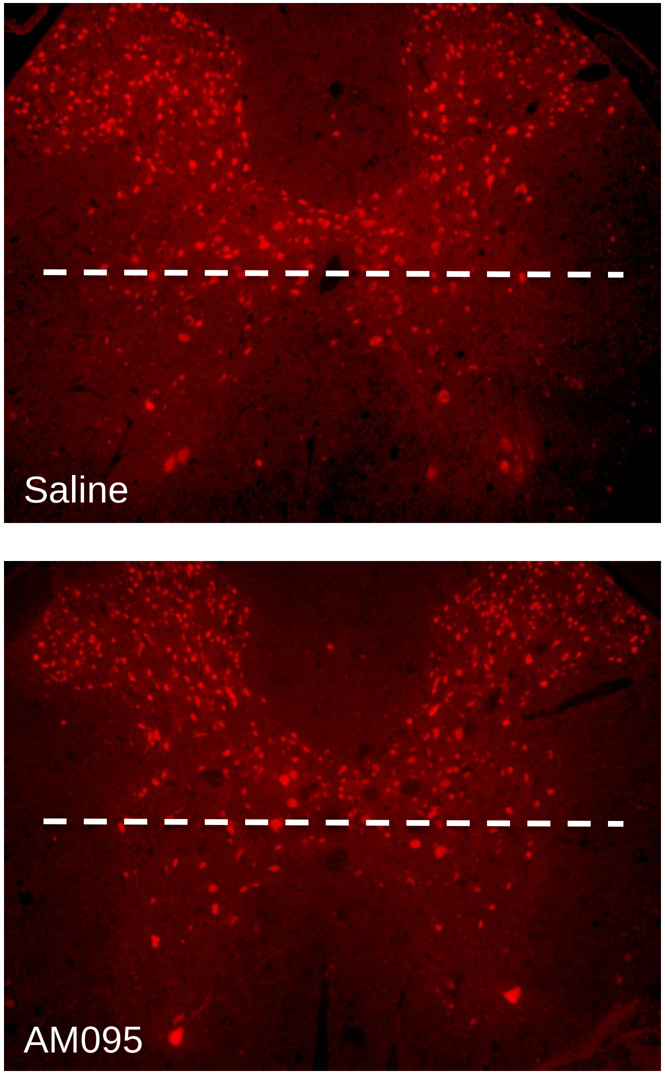
LPA receptor 1





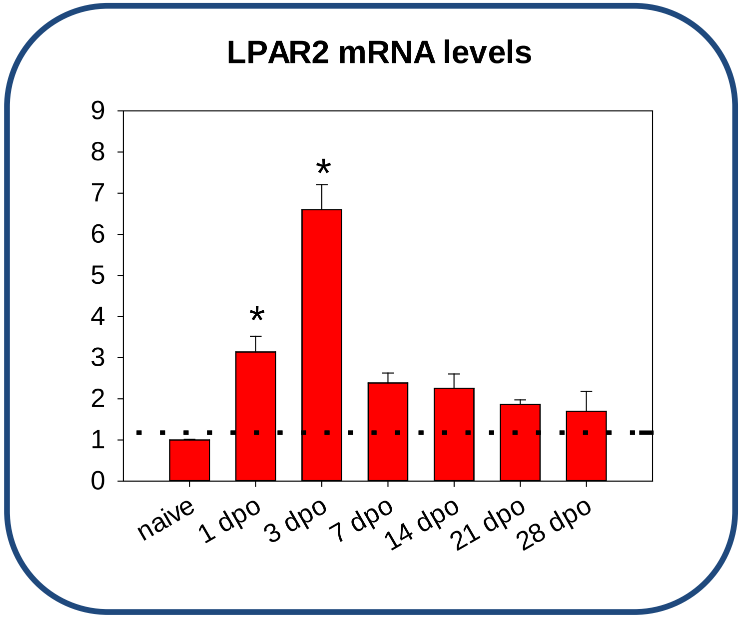
* $p < 0.05$

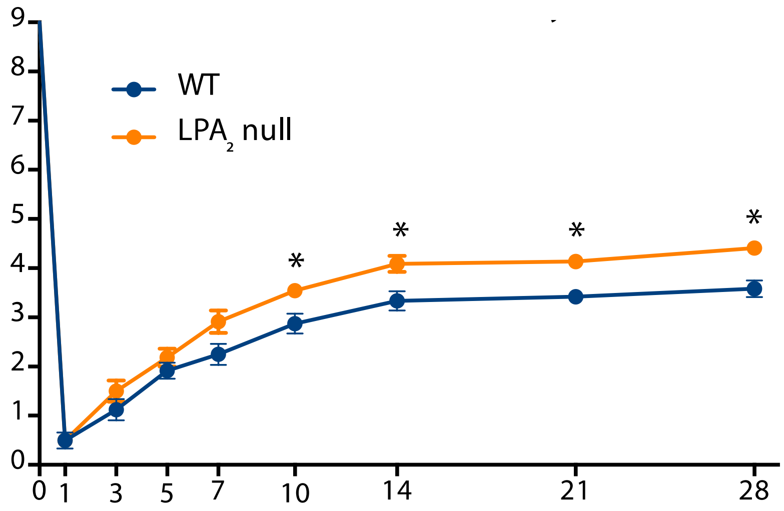
600 µm Rostral

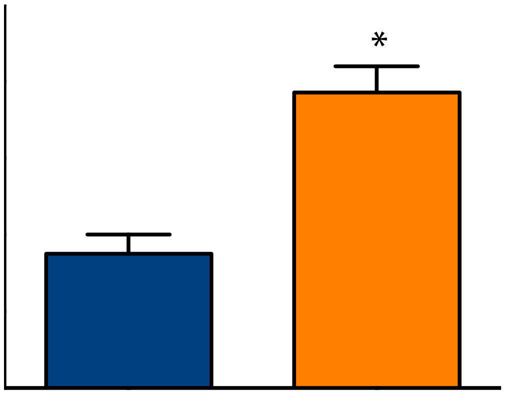


Santos-Nogueira et al., 2015 J Neurosci

LPA receptor 2

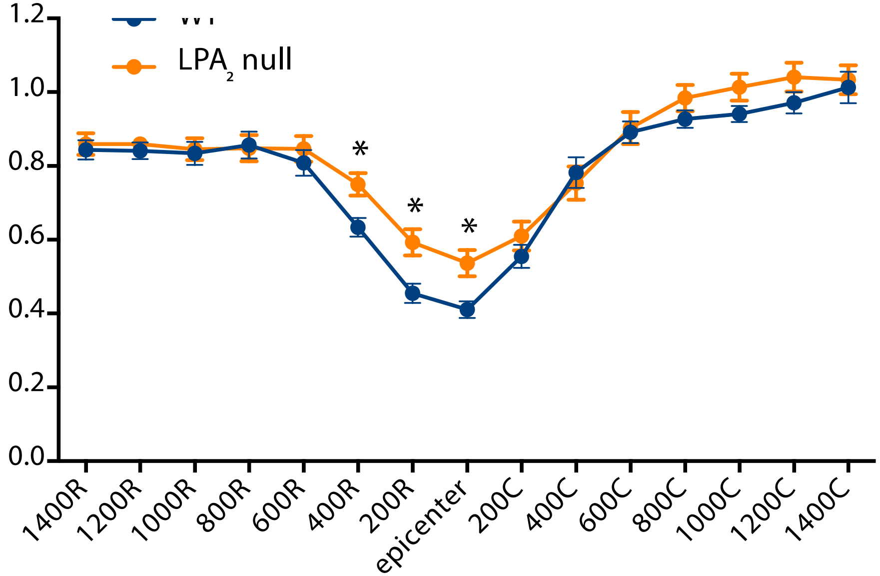




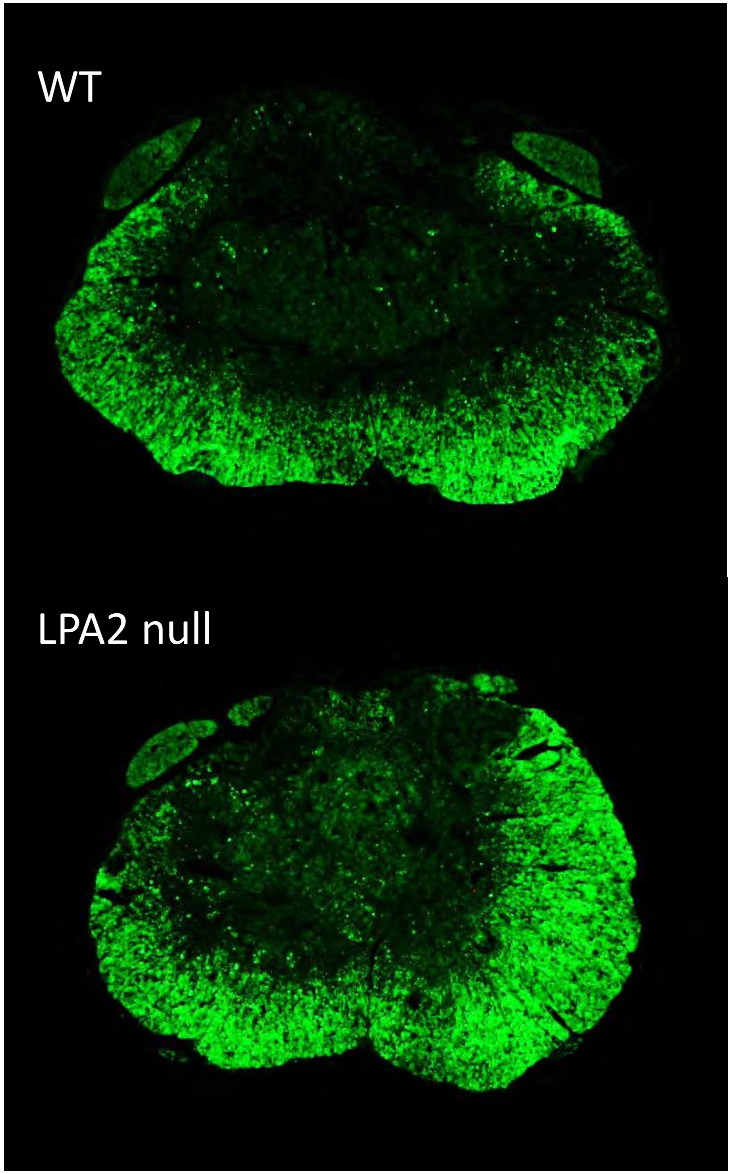


Lopez-Serrano et al., Brain Beh Immun 2019

LPA receptor 2



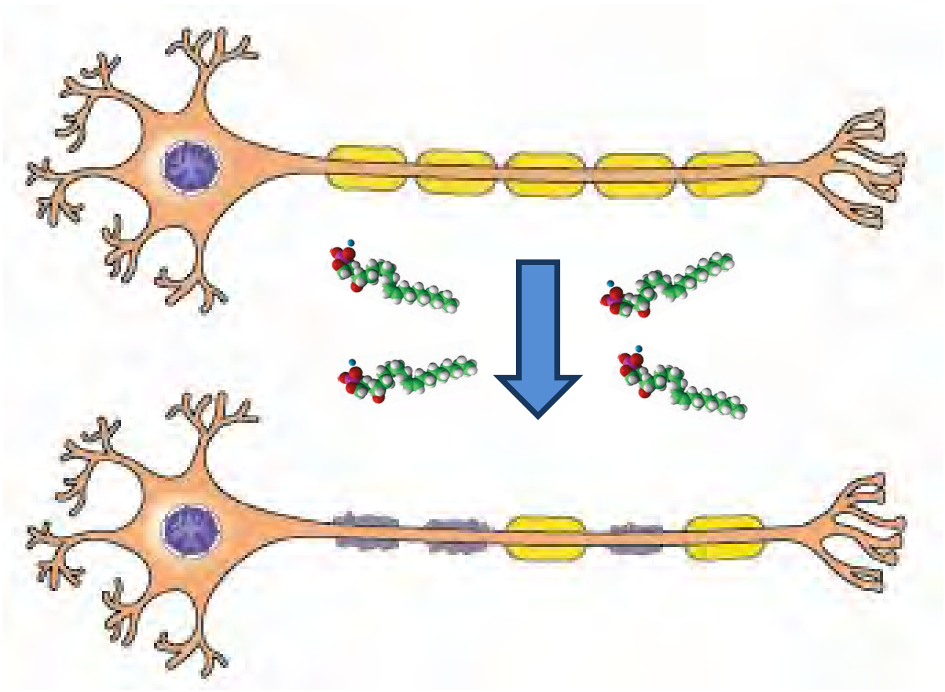
* $p < 0.05$



Lopez-Serrano et al., Brain Beh Immun 2019

LPA receptor 1

How does LPA-LPA$_1$ signaling induce demyelination in the spinal cord?



Lysophosphatidic acid

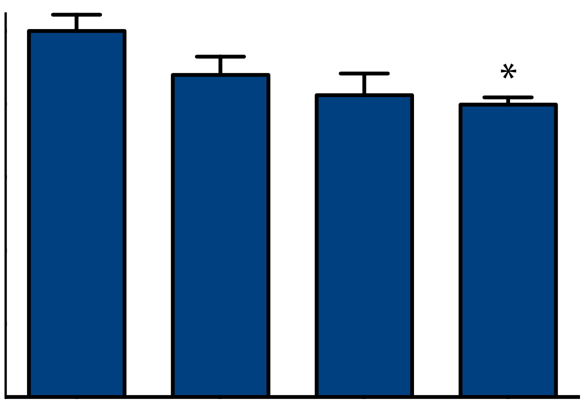
OLIGODENDROCYTE SURVIVAL: *in vitro* studies

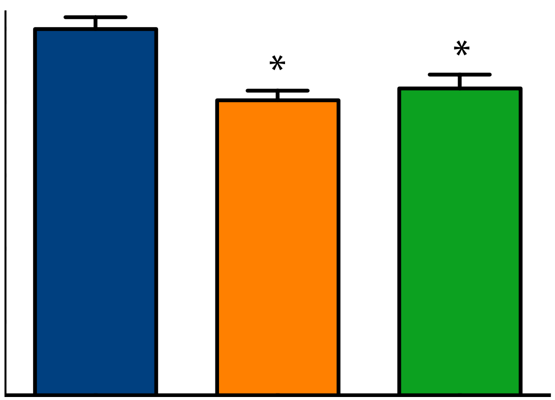
OL ENRICHED
CULTURE

LPA exposure

(for 24h)

Control
LPA (0.01, 0.1, 1μM)



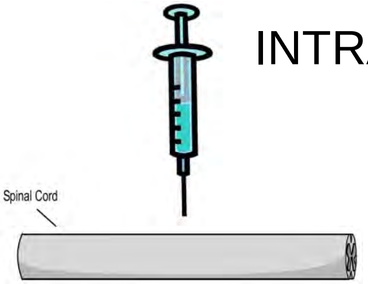


* $p < 0.05$

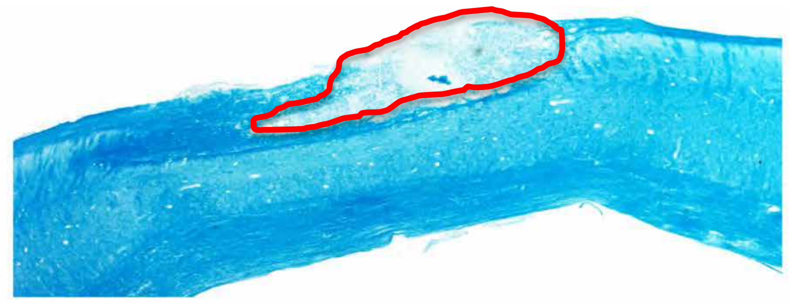
Santos-Nogueira et al., 2015 J Neurosci

LPA receptor 1

INTRASPINAL INJECTION OF LYSOPHOSPHATIDIC ACID

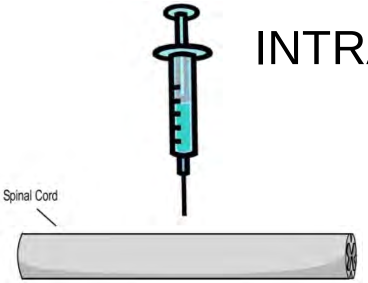


Myelin
(LFB)



Santos-Nogueira et al., 2015 J Neurosci

LPA receptor 1

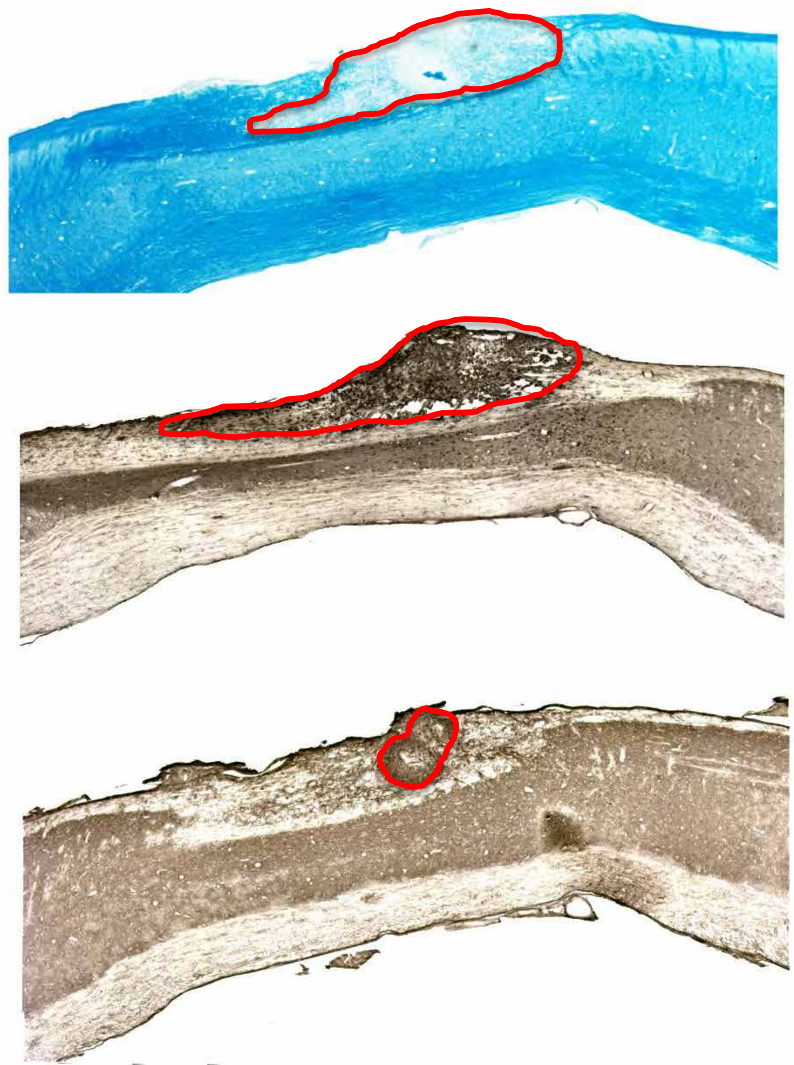


INTRASPINAL INJECTION OF LYSOPHOSPHATIDIC ACID

Myelin
(LFB)

Microglia and
macrophages
(Iba1)

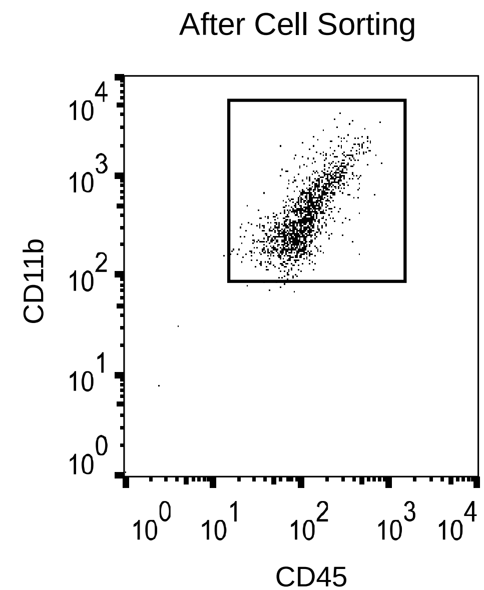
Astrocytes
(GFAP)

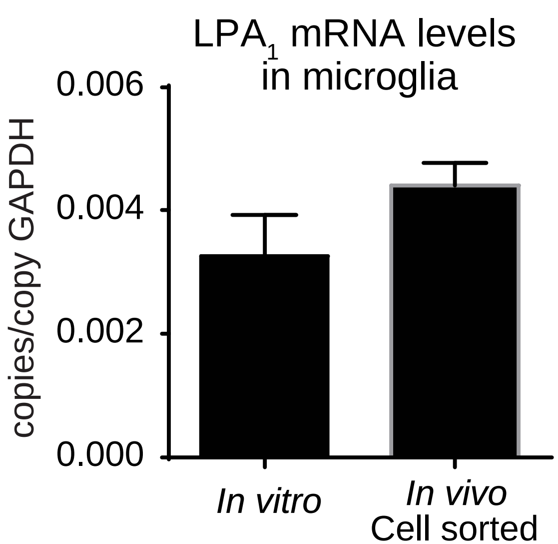


Santos-Nogueira et al., 2015 J Neurosci

LPA receptor 1

CD11b immunopanning – – – – ▸ Cell sorting



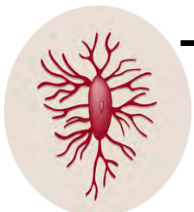


Santos-Nogueira et al., 2015 J Neurosci

LPA receptor 1

OLIGODENDROCYTE SURVIVAL: *in vitro* studies

MICROGLIA
CULTURE



→ Generation of conditioned medium

- Control
- 1μM LPA
- 1μM LPA + 12.5μM AM095

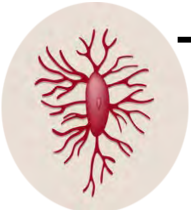
→ OL exposure to conditioned medium (for 24h)

Santos-Nogueira et al., 2015 J Neurosci

LPA receptor 1

OLIGODENDROCYTE SURVIVAL: *in vitro* studies

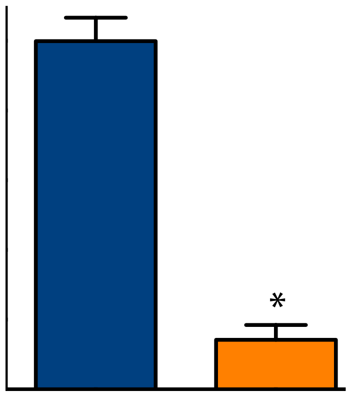
MICROGLIA
CULTURE

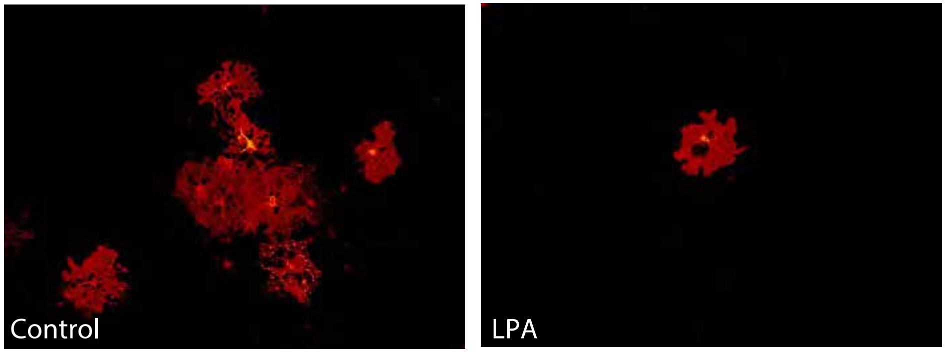


Generation of conditioned medium

Control
1μM LPA
1μM LPA + 12.5μM AM095

OL exposure to conditioned medium (for 24h)





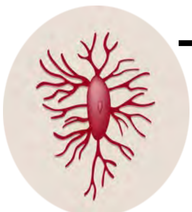
* $p < 0.05$ vs. control
\# $p < 0.05$ vs. LPA

Santos-Nogueira et al., 2015 J Neurosci

LPA receptor 1

OLIGODENDROCYTE SURVIVAL: *in vitro* studies

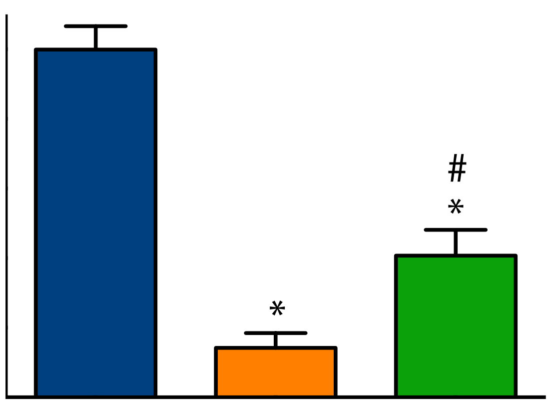
MICROGLIA
CULTURE



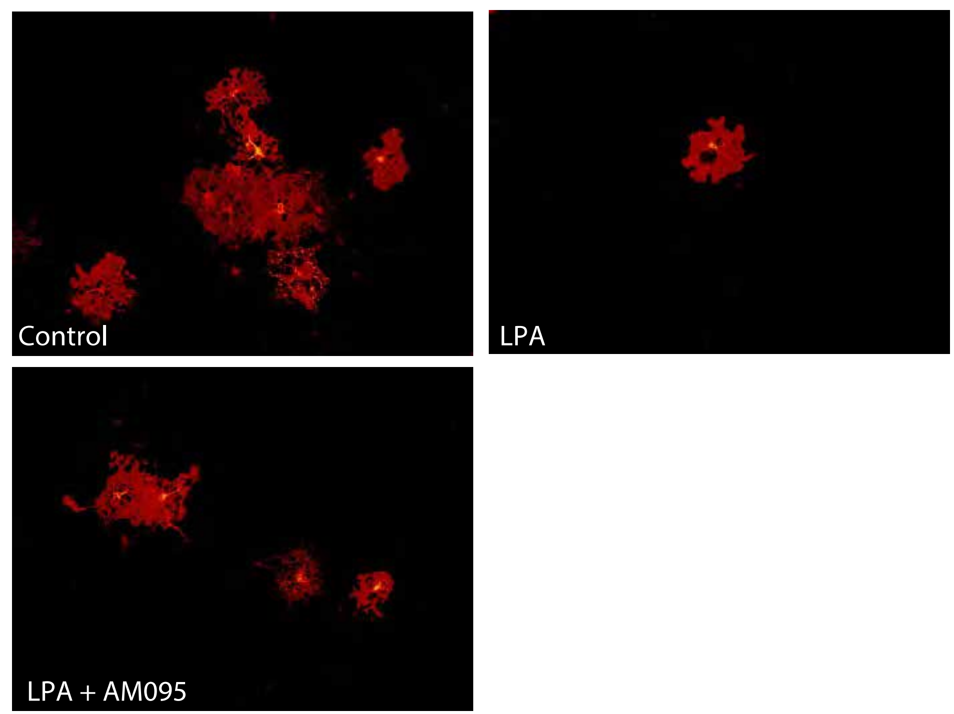
→ Generation of conditioned medium

- Control
- 1μM LPA
- 1μM LPA + 12.5μM AM095

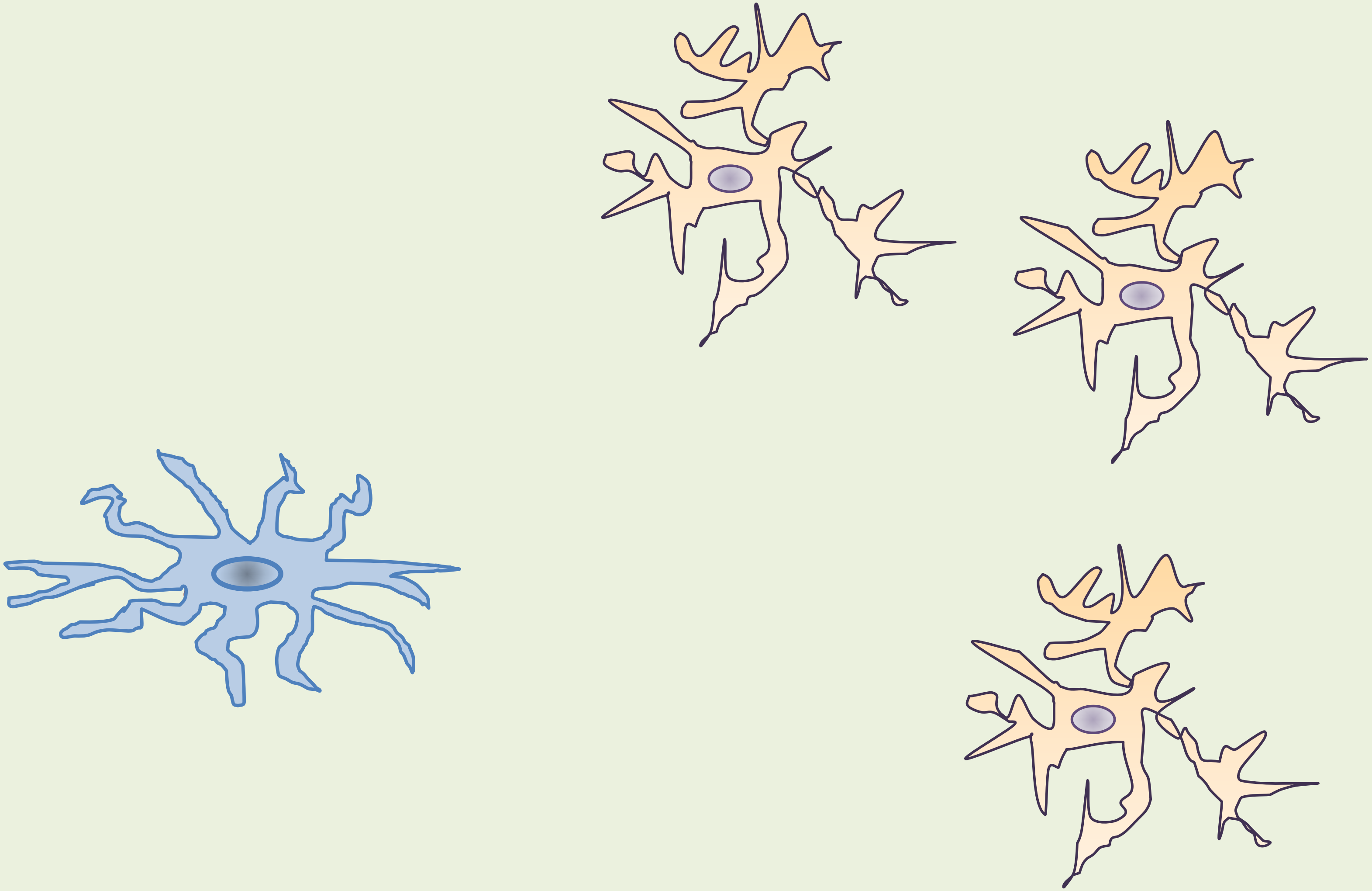
→ OL exposure to conditioned medium (for 24h)



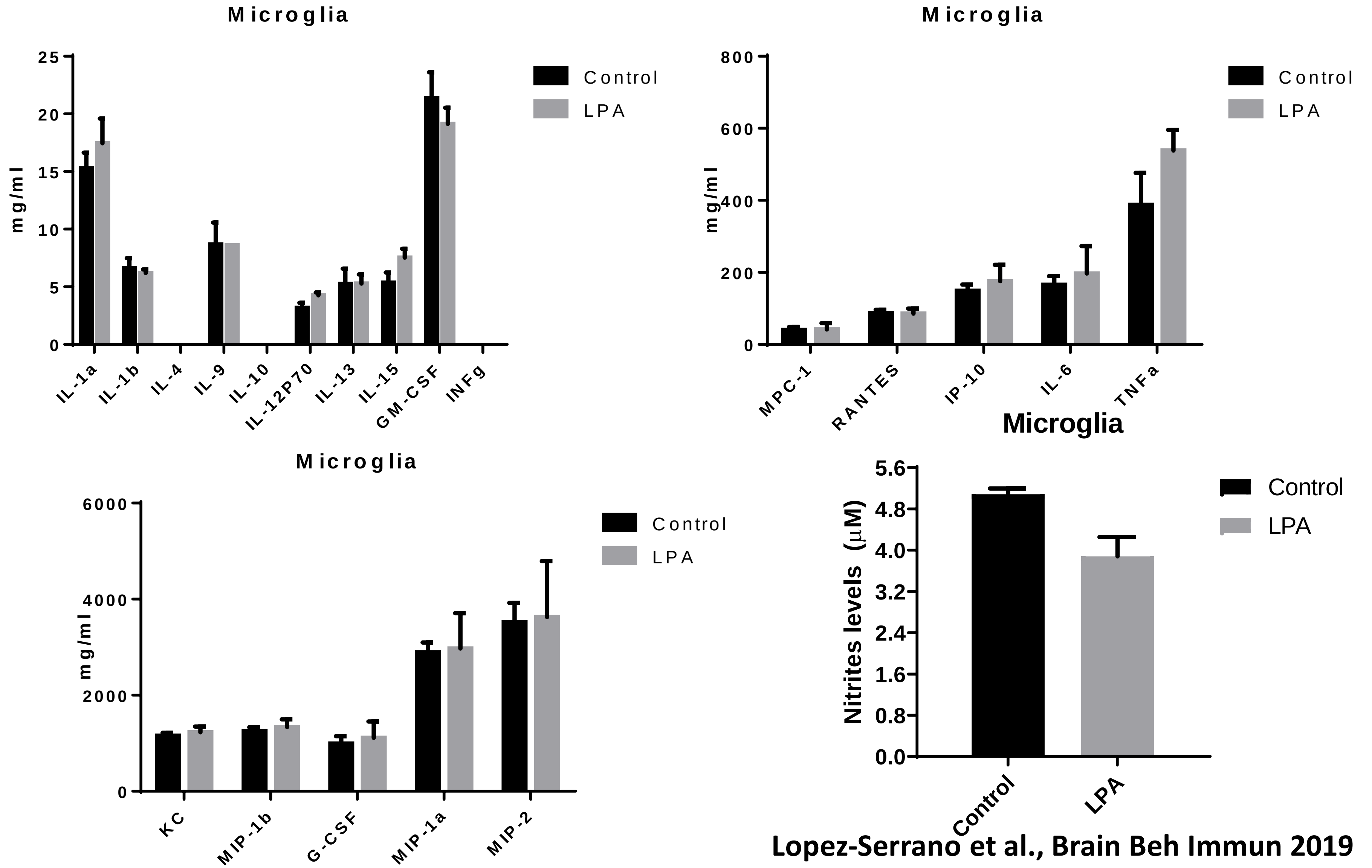
* $p < 0.05$ vs. control
# $p < 0.05$ vs. LPA



Santos-Nogueira et al., 2015 J Neurosci



How does microglia induce oligodendrocyte cell death upon LPA stimulation?

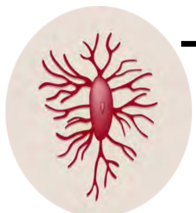


Lopez-Serrano et al., Brain Beh Immun 2019

How does microglia induce oligodendrocyte cell death upon LPA stimulation?

Brilliant Blue G (BBG)

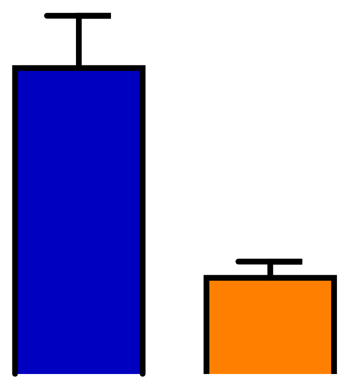
MICROGLIA
CULTURE



Generation of conditioned medium

Control
1μM LPA

OL exposure to conditioned medium
(for 24h)



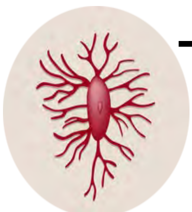
* $p < 0.001$ vs. control
# $p < 0.05$ vs. LPA vehicle

Lopez-Serrano et al., Brain Beh Immun 2019

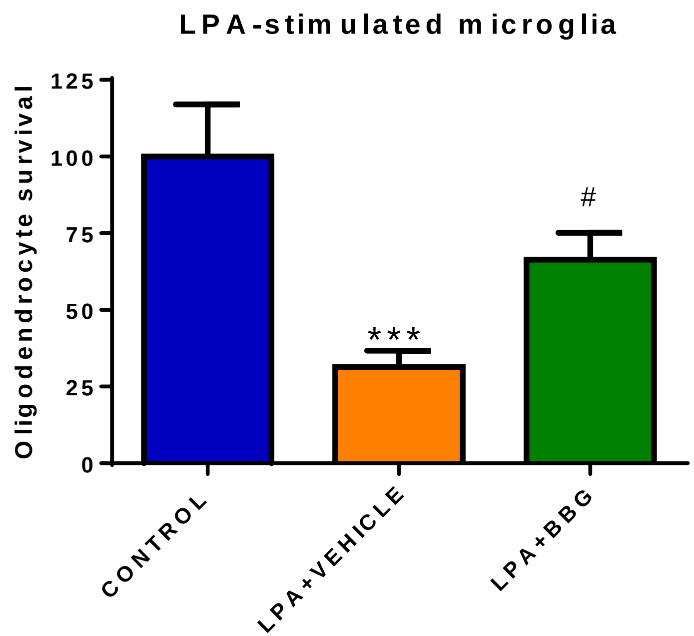
How does microglia induce oligodendrocyte cell death upon LPA stimulation?

Brilliant Blue G (BBG)

MICROGLIA
CULTURE

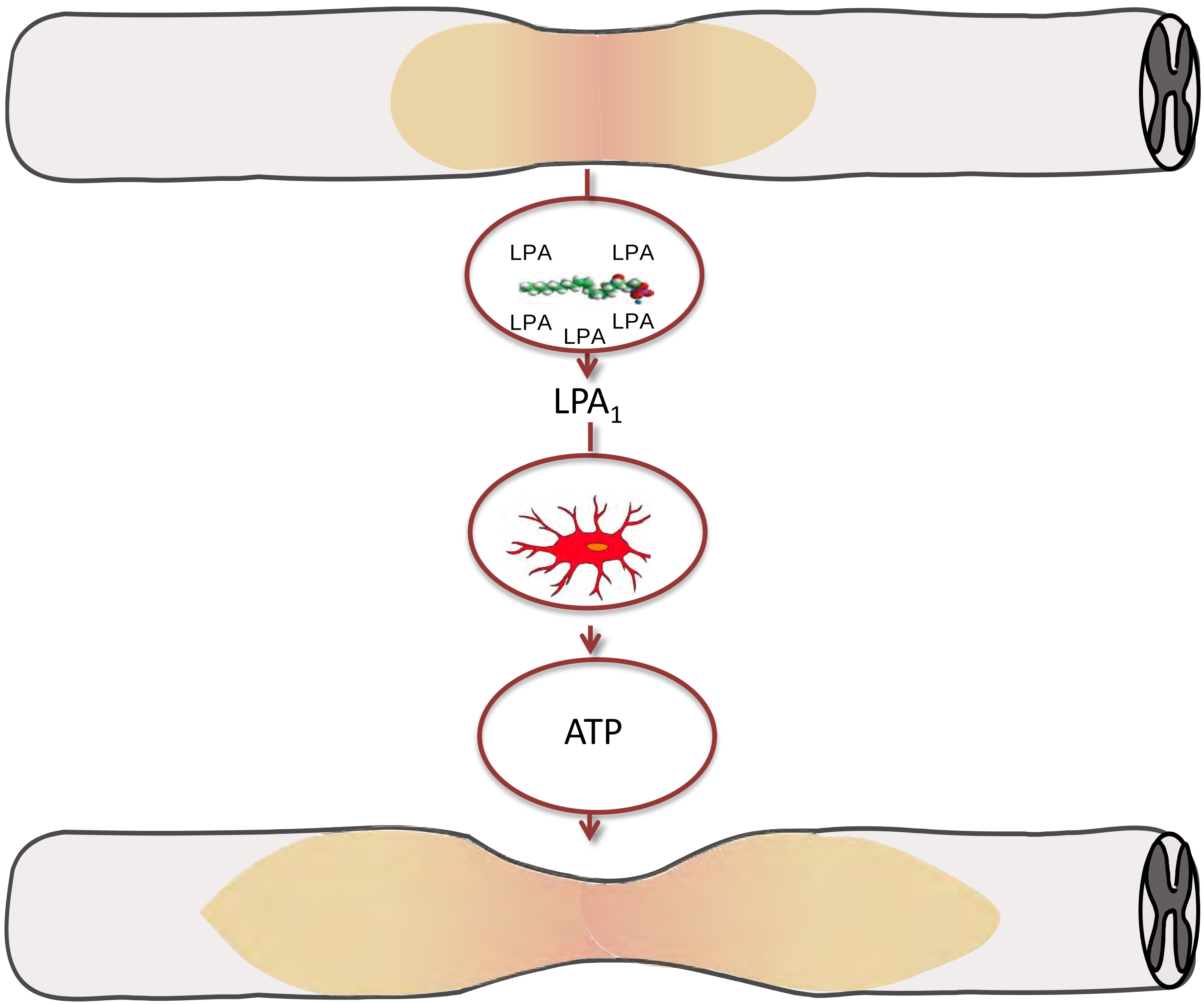


→ Generation of conditioned medium { Control / 1μM LPA → OL exposure to conditioned medium (for 24h)

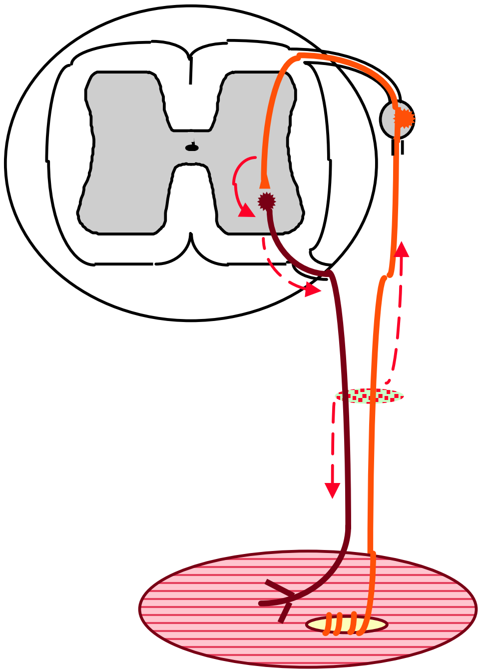


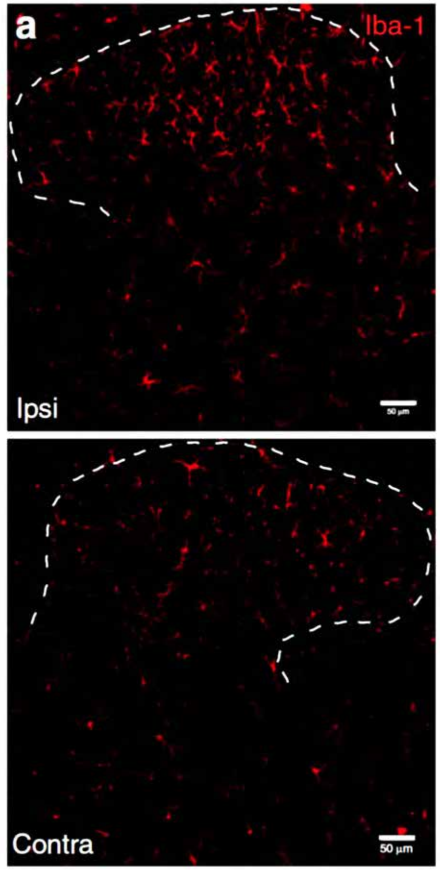
* $p < 0.001$ vs. control
\# $p < 0.05$ vs. LPA vehicle

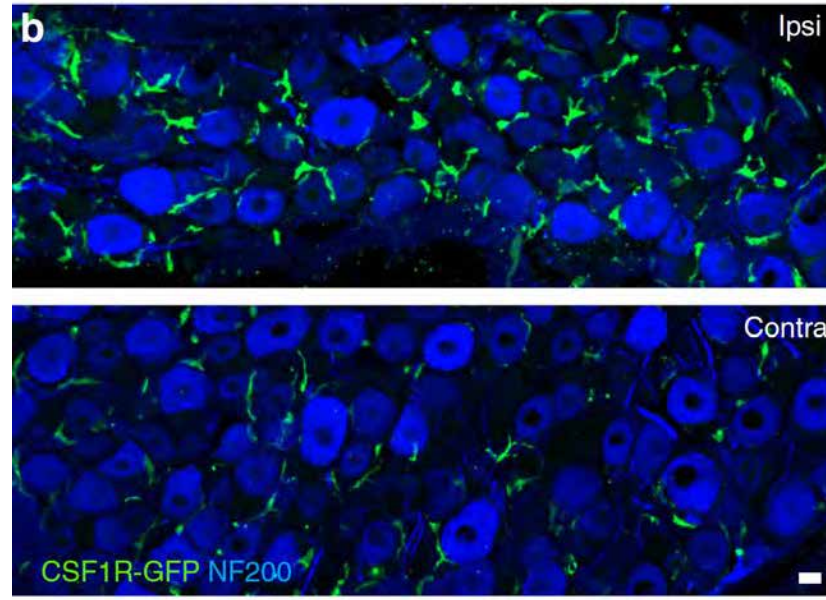
Lopez-Serrano et al., Brain Beh Immun 2019

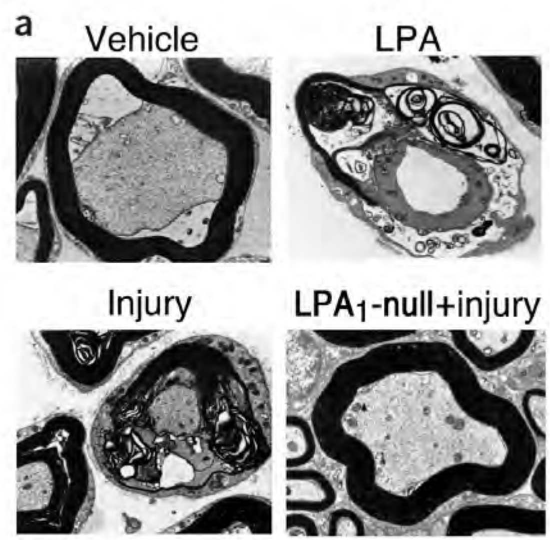

LPA
LPA
LPA
LPA
LPA
LPA_1
ATP

LPA receptor 1 after sciatic nerve injury



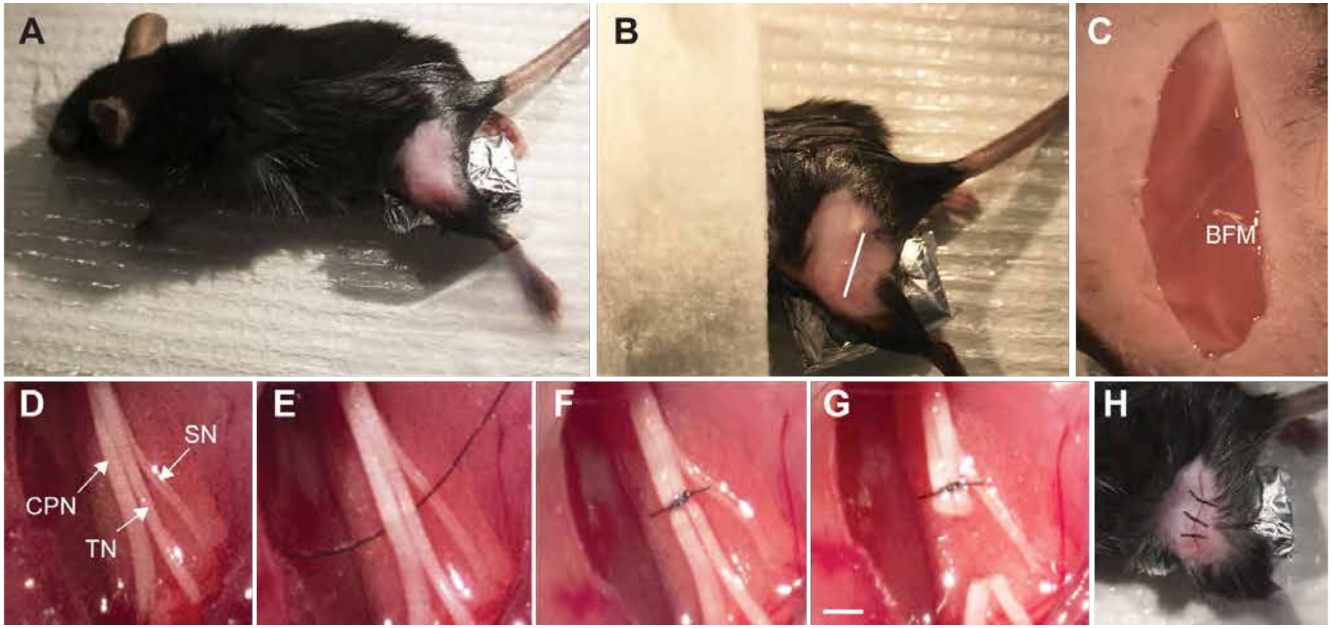


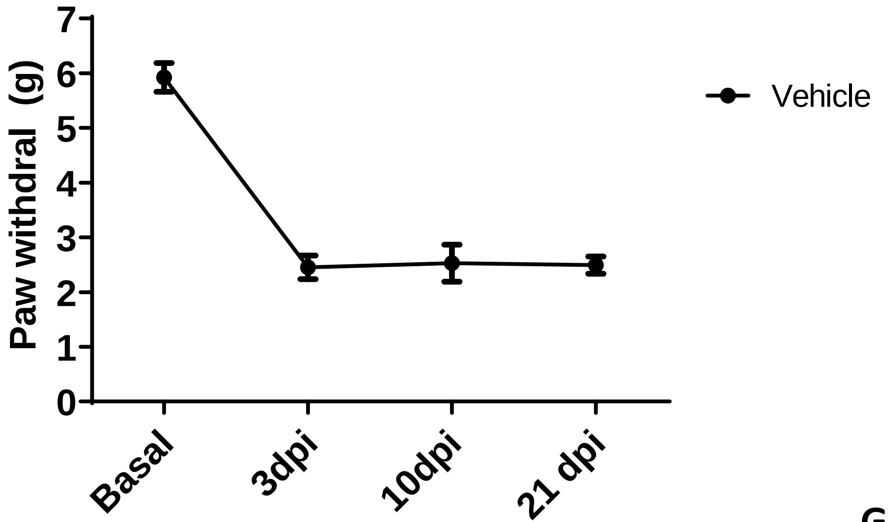


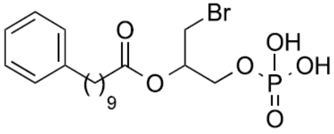


Yu et al., 2020; Unue et al., 2007

LPA receptor 1 after sciatic nerve injury

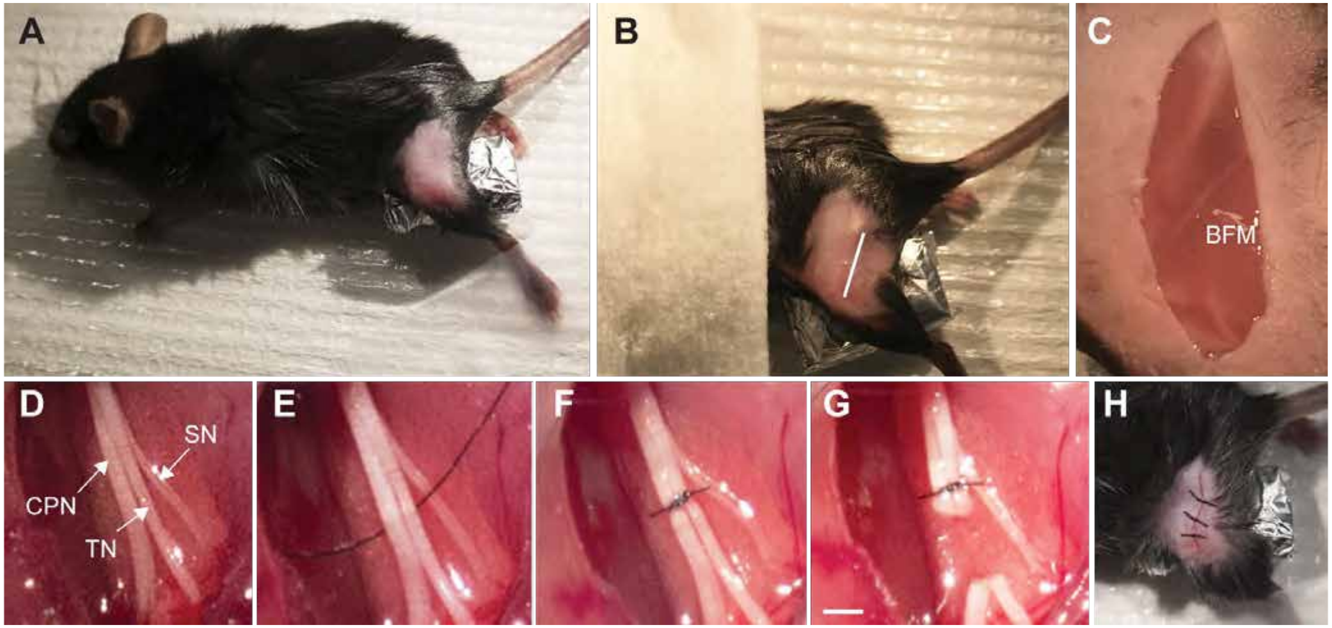




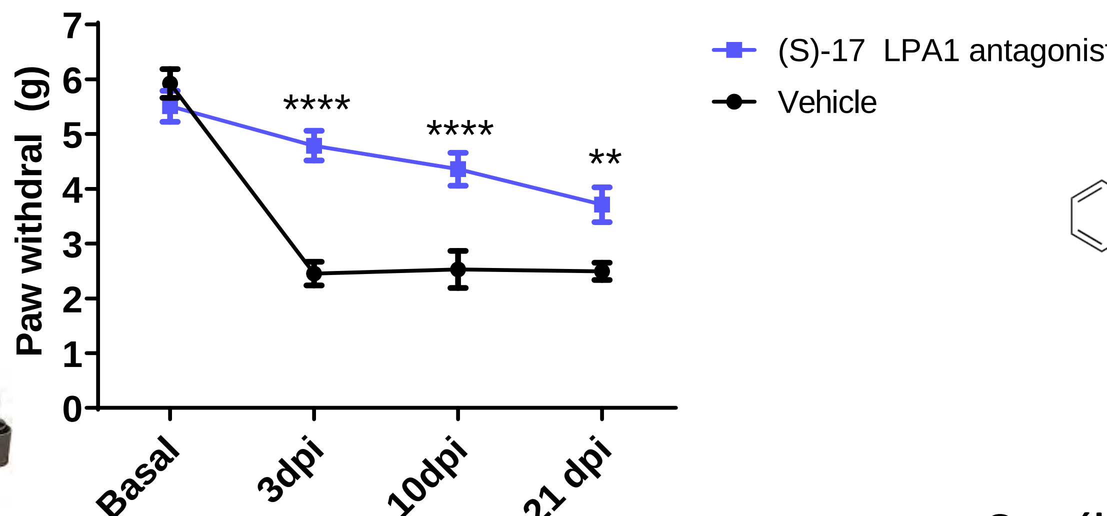


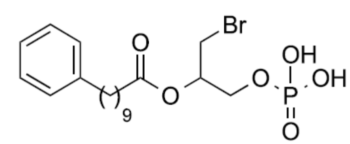
González-Gil et al., 2021

LPA receptor 1 after sciatic nerve injury



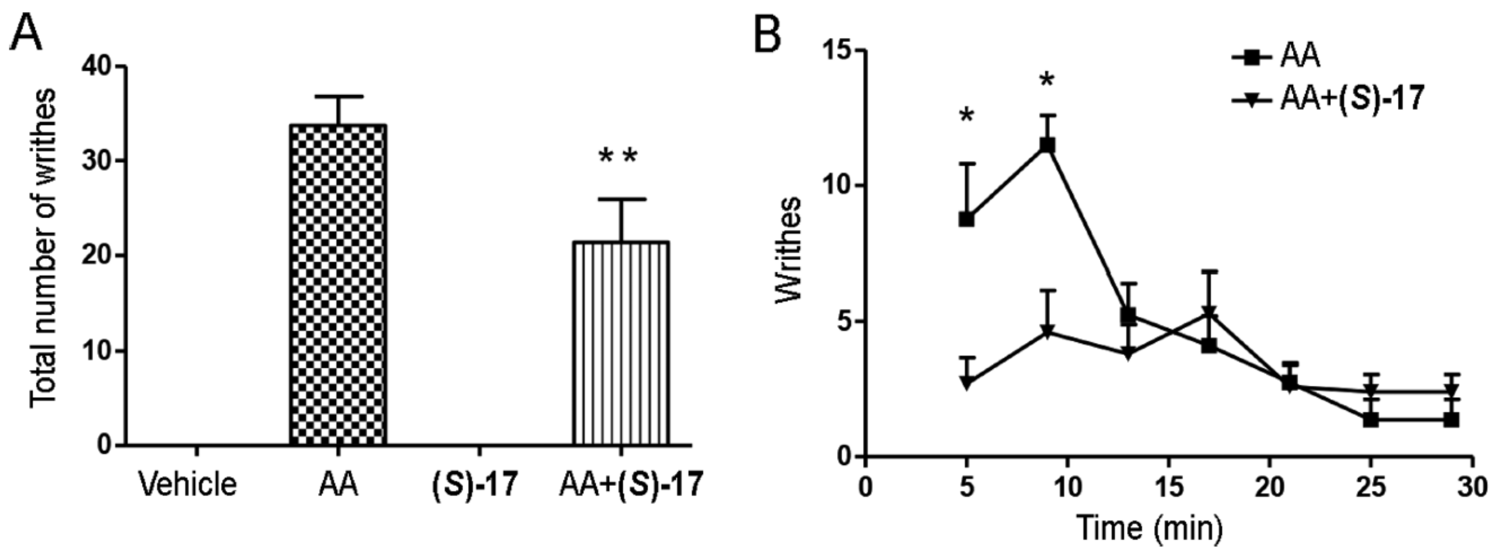
Mechanical threshold

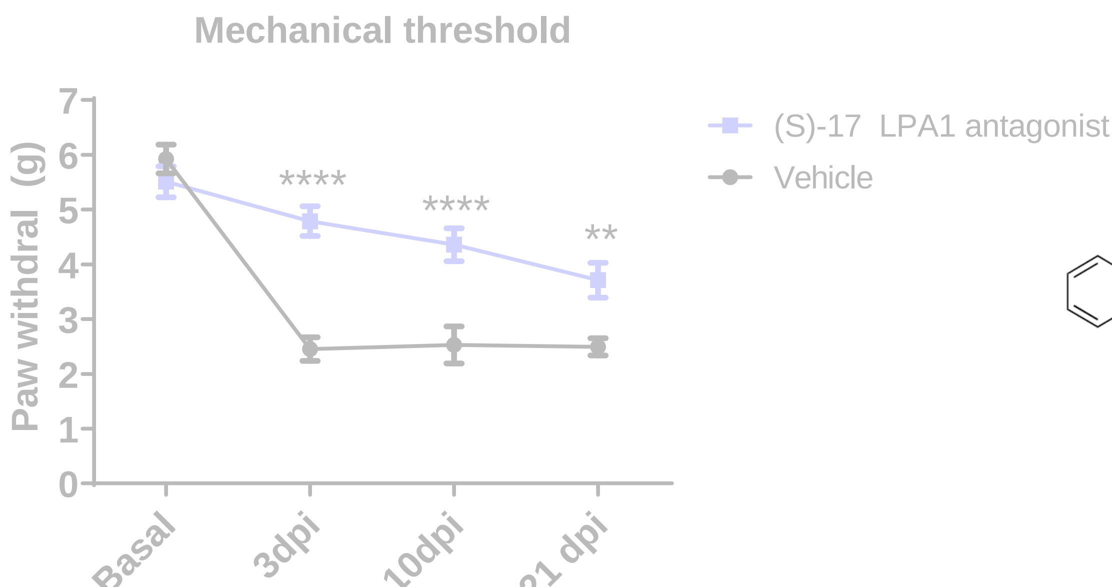


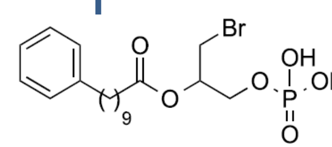


González-Gil et al., 2021

LPA receptor 1 after sciatic nerve injury







González-Gil et al., 2021

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