ÁREA: NEUROCIENCIAS

Grupos:

Grupo de Neurología

Responsable: José M. Serratosa Fernández
IP: Marina Sánchez García
Investigación: Básica y Clínica

Grupo de Psiquiatría y Salud Mental

Responsable: Enrique Baca García
Investigación: Clínica

Grupo de Señalización Mitocondrial del Calcio

Responsable: Jorgina Satrústegui Gil-Delgado
Investigación: Básica

ÁREA: NEUROCIENCIAS

NOMBRE DEL GRUPO: **Señalización Mitocondrial del Calcio**

PONENTE: Beatriz Pardo

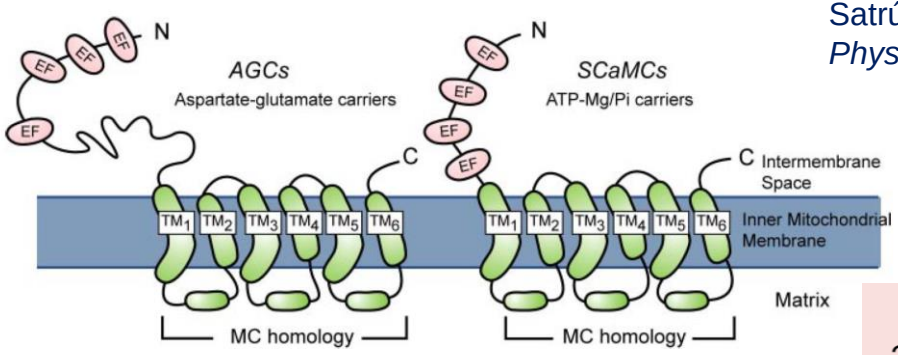
DATOS DE CONTACTO: bpardo@cbm.csic.es, jsatrustegui@cbm.csic.es, adelarco@cbm.csic.es

“Deficiencia en Aralar/AGC1: tratamiento con dieta cetogénica y cuerpos cetónicos"

Aralar/AGC1/SlC25a12: Structure and activation by cytosolic Ca^{2+}

$S_{0.5}$
Brain = 324 nM

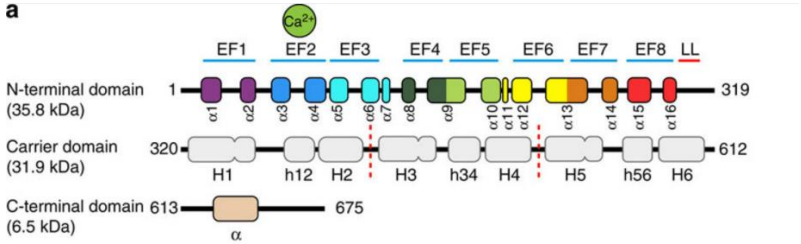
AGC1/Aralar
Skeletal Muscle
Heart
Brain



Satrústegui, Pardo & del Arco, *Physiol. Rev.* (2007)

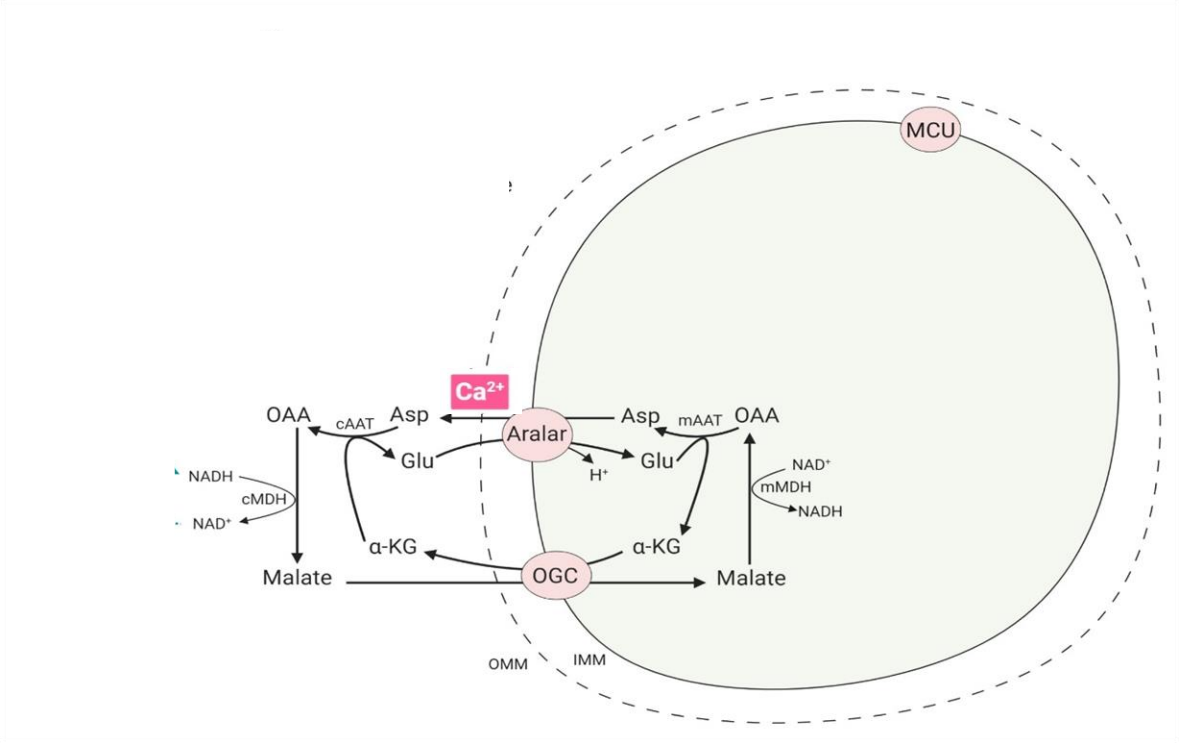
$S_{0.5}$
3-4 µM

AGC2/Citrin Liver
Heart

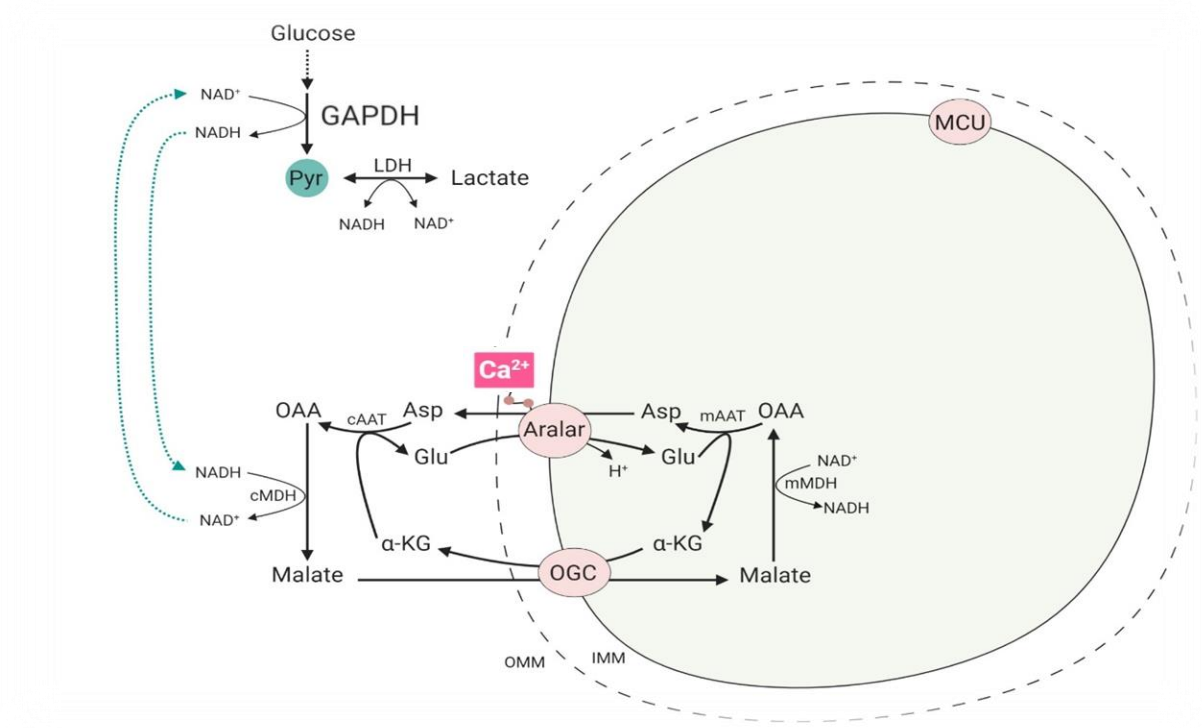


Modified from Thangaratnarajah, C., Ruprecht, J. J., & Kunji, E. R. (2014)

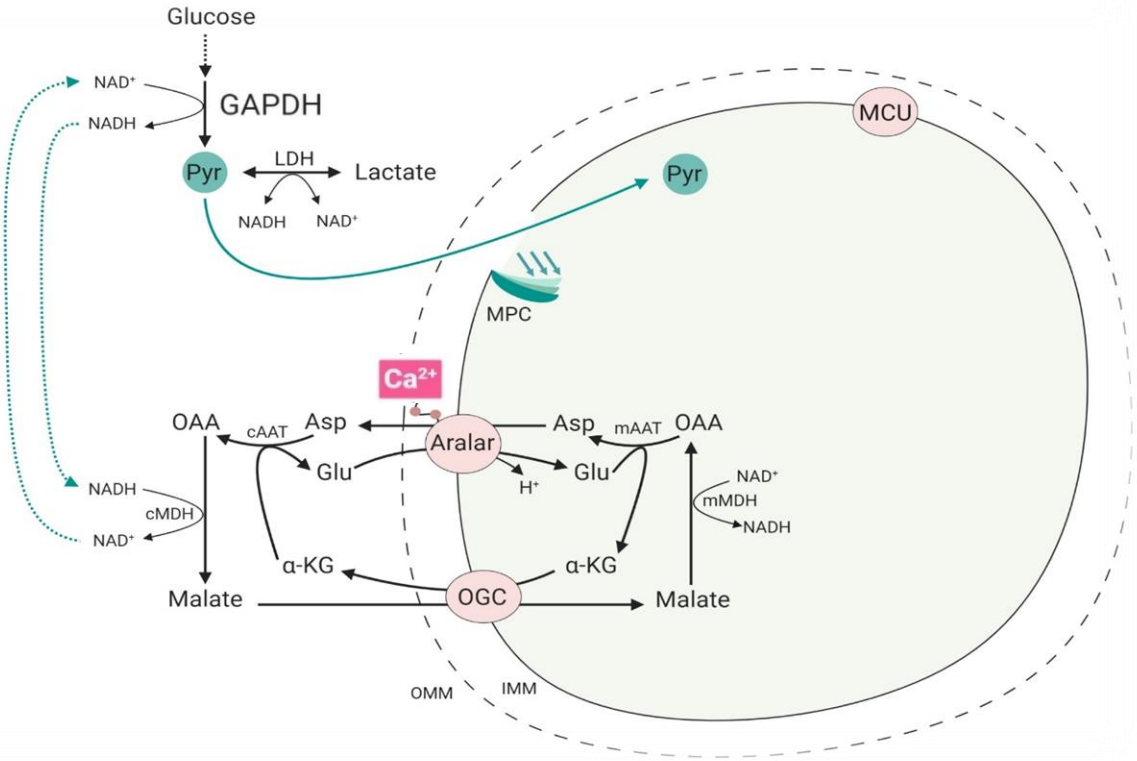
Aralar/Slc25a12 as the regulatory component of the NADH malate-aspartate shuttle(MAS)



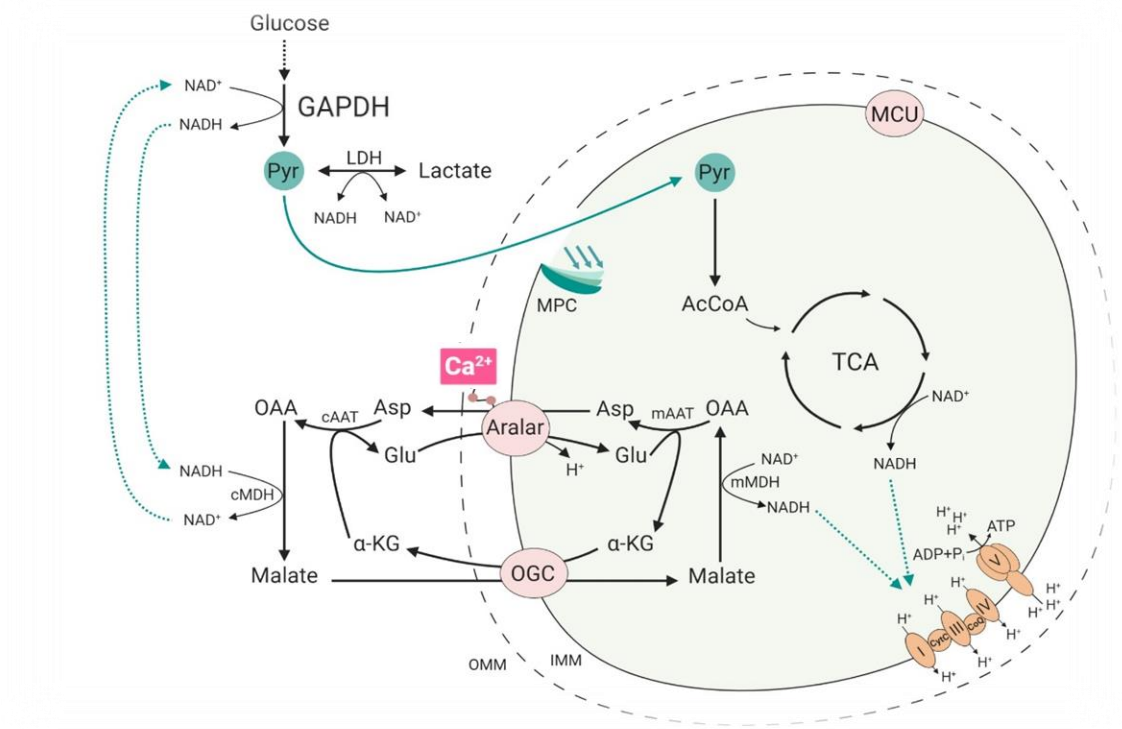
Aralar-MAS enables glycolysis to flow regenerating cytosolic NAD^+



Aralar-MAS provides substrates to neuronal mitocondrial for respiration

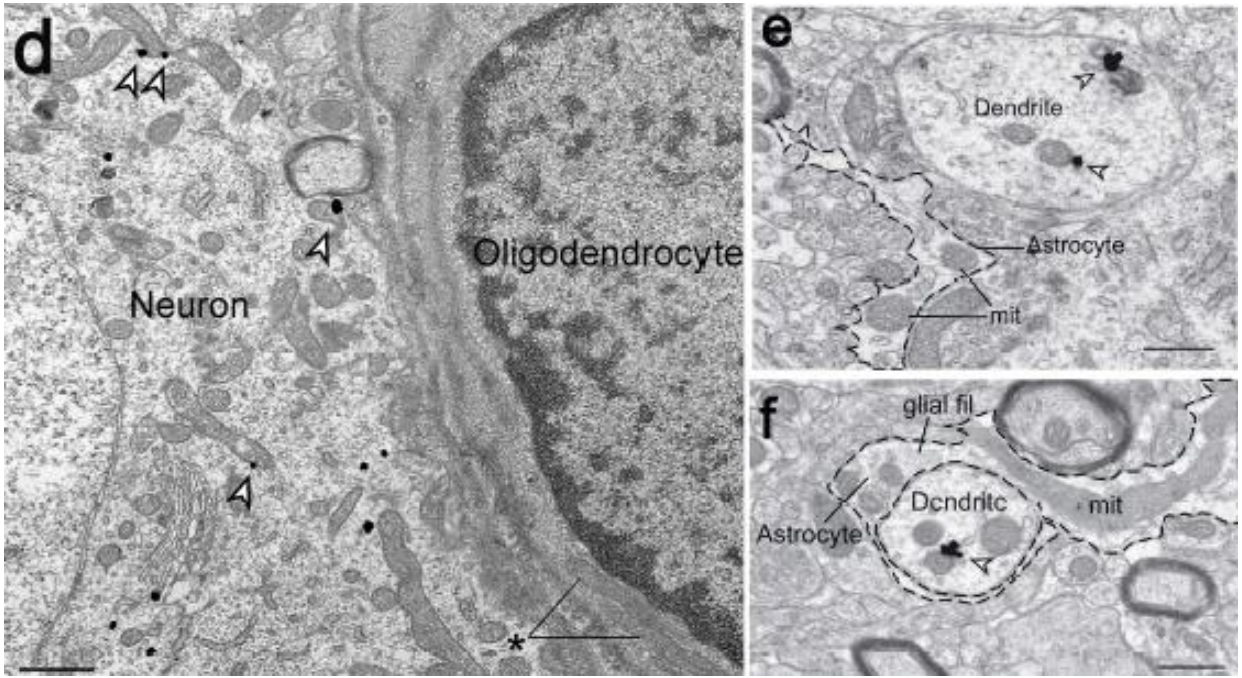


Aralar-MAS provides substrates to neuronal mitocondrial for respiration



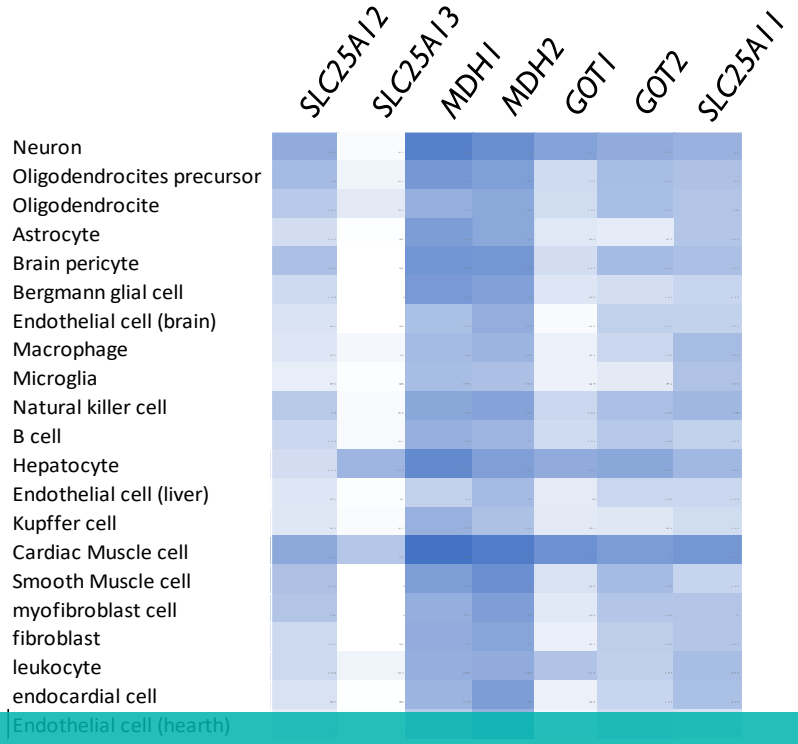
Brain Aralar-Slc25a12 is mainly/abundantly localized in neuronal mitochondria

Aralar-immunogold labeling in neurons: neurons (93.1% ± 18.0%) glia (7 % ± 0.5%)

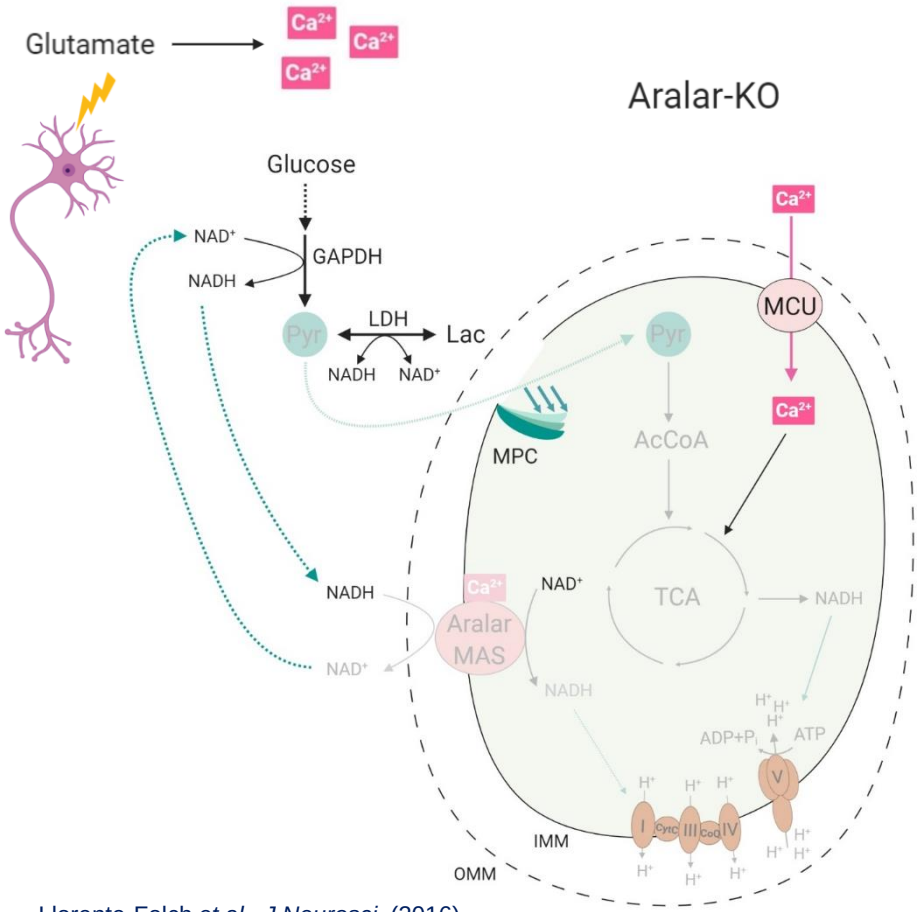


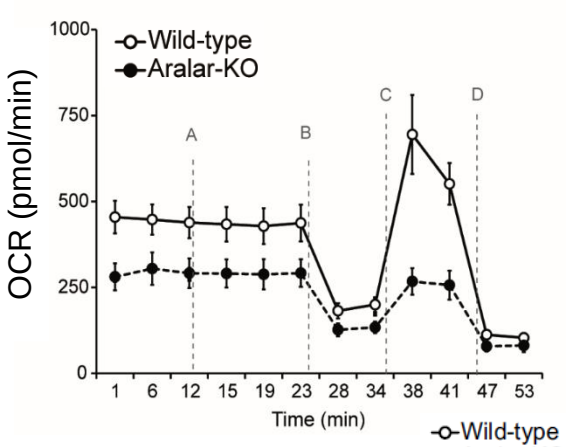
Pardo *et al*, *JCBFM* 2011

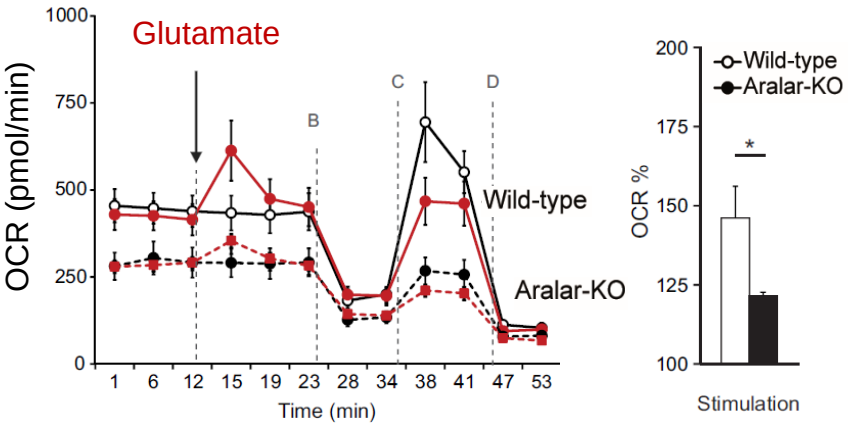
Expression of MAS components AGC (AGC1/Slc25a12; or AGC2/Slc25a13), OGC (Slc25a11) and the enzymes (GOT1, GOT2, MDH1, MDH2) in cells and tissues



Mitochondrial respiration is drastically reduced in Aralar-KO neurons

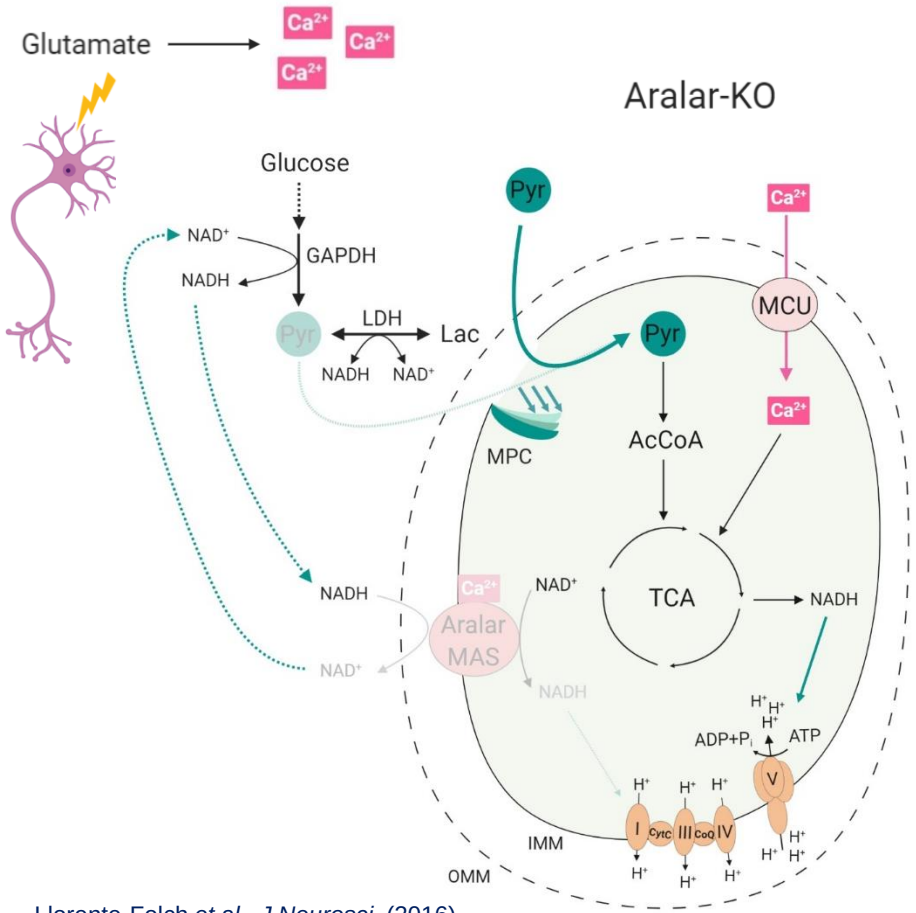


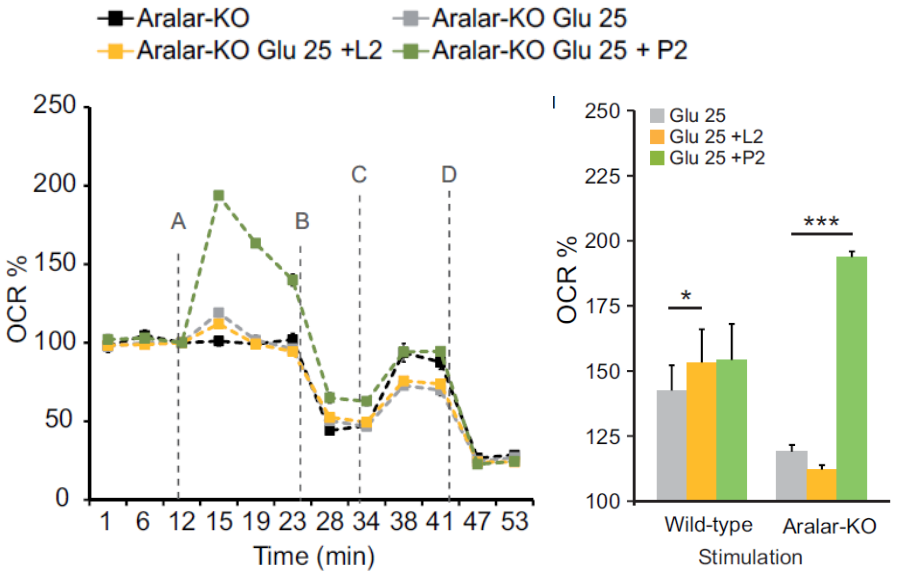




Llorente-Folch *et al*., *J Neurosci*. (2016)

Pyruvate recovers mitocondrial respiration in Aralar-KO neurons

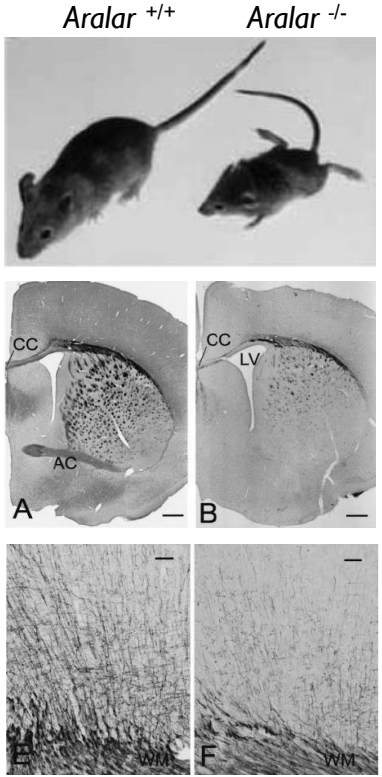




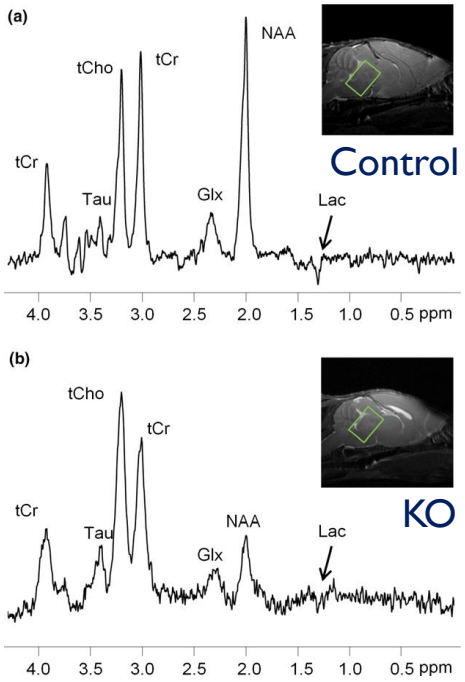
Llorente-Folch *et al*., *J Neurosci.* (2016)

Characteristics/Phenotype of Aralar-KO mice

- Short lifespan(PND20)
- Delayed development
- Hypomyelination
- Epilepsy, seizures
- Tremor, lack of motor coordination
- Ataxic posture
- Decreased Aspartate and NAA



Global Aralar – KO mice. (Jalil *et al.*, 2005; Ramos *et al.*, 2011)



(Juaristi *et al.*, 2013)

Aralar/AGC1 deficiency: Early infantile epileptic encephalopathy 39

AGC1 Deficiency Associated with Global Cerebral Hypomyelination

Rolf Wibom, Ph.D., Francesco M. Lasorsa, Ph.D., Virpi Töhönen, Ph.D., Michela Barbaro, Ph.D., Fredrik H. Sterky, M.D., Thomas Kucinski, M.D., Ph.D., Karin Naess, M.D., Monica Jonsson, M.D., Ciro L. Pierri, Chem.D., Ferdinando Palmieri, M.D., and Anna Wedell, M.D., Ph.D.

N ENGL J MED 361;5 NEJM.ORG JULY 30, 2009

AGC1 Deficiency Causes Infantile Epilepsy, Abnormal Myelination, and Reduced *N*-Acetylaspartate

Marni J. Falk • Dong Li • Xiaowu Gai • Elizabeth McCormick • Emily Place • Francesco M. Lasorsa • Frederick G. Otieno • Cuiping Hou • Cecilia E. Kim • Nada Abdel-Magid • Lyam Vazquez • Frank D. Mentch • Rosetta Chiavacci • Jinlong Liang • Xuanzhu Liu • Hui Jiang • Giulia Giannuzzi • Eric D. Marsh • Guo Yiran • Lifeng Tian • Ferdinando Palmieri • Hakon Hakonarson

Expanding Phenotypic Spectrum of Cerebral Aspartate–Glutamate Carrier Isoform 1 (AGC1) Deficiency

Brian Pfeiffer[1,2] Kuntal Sen[3] Shagun Kaur[1,2] Kara Pappas[2,4,5]

Neuropediatrics October 6, 2019

Case Report
A Novel Nonsense Gene Variant Responsible for Early Infantile Epileptic Encephalopathy Type 39: Case Report

Maysa Saleh, Mostafa Helmi and Bushra Yacop

Pediatrician, Dubai Health Authority, United Arab Emirates

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A WILEY

Longitudinal MRI findings in patient with *SLC25A12* pathogenic variants inform disease progression and classification

Brian C. Kavanaugh[1,2] | Emily B. Warren[3] | Ozan Baytas[1,2,3] | Michael Schmidt[1,2,3] | Derek Merck[4] | Karen Buch[5] | Judy S. Liu[3,6,7] | Chanika Phornphutkul[8] | Paul Caruso[5] | Eric M. Morrow[1,2,3,7]

Seizure: European Journal of Epilepsy 69 (2019) 154–172

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

The landscape of early infantile epileptic encephalopathy in a consanguineous population

Marwan Nashabat[a,1], Xena S. Al Qahtani[b,1], Salwa Almakdob[c], Waleed Altwaijri[d], Duaa M. Ba-Armah[d], Khalid Hundallah[b], Amal Al Hashem[e,f], Saeed Al Tala[g], Sateesh Maddirevula[h], Fowzan S. Alkuraya[f,h,i], Brahim Tabarki[b], Majid Alfadhel[g,*]

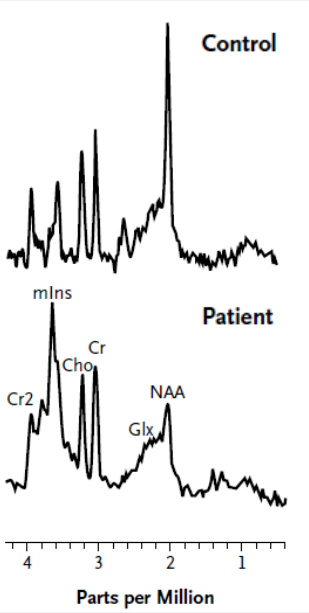
Pronicka et al. J Transl Med (2016) 14:174
DOI 10.1186/s12967-016-0930-9

Journal of Translational Medicine

RESEARCH Open Access

New perspective in diagnostics of mitochondrial disorders: two years' experience with whole-exome sequencing at a national paediatric centre

Ewa Pronicka[1,2*], Dorota Piekutowska-Abramczuk[1†], Elżbieta Ciara[1†], Joanna Trubicka[1†], Dariusz Rokicki[2], Agnieszka Karkucińska-Więckowska[3], Magdalena Pajdowska[4], Elżbieta Jurkiewicz[5], Paulina Halat[1], Joanna Kosińska[6], Agnieszka Pollak[7], Małgorzata Rydzanicz[6], Piotr Stawiński[7], Maciej Pronicki[3], Małgorzata Krajewska-Walasek[1] and Rafał Płoski[6*]

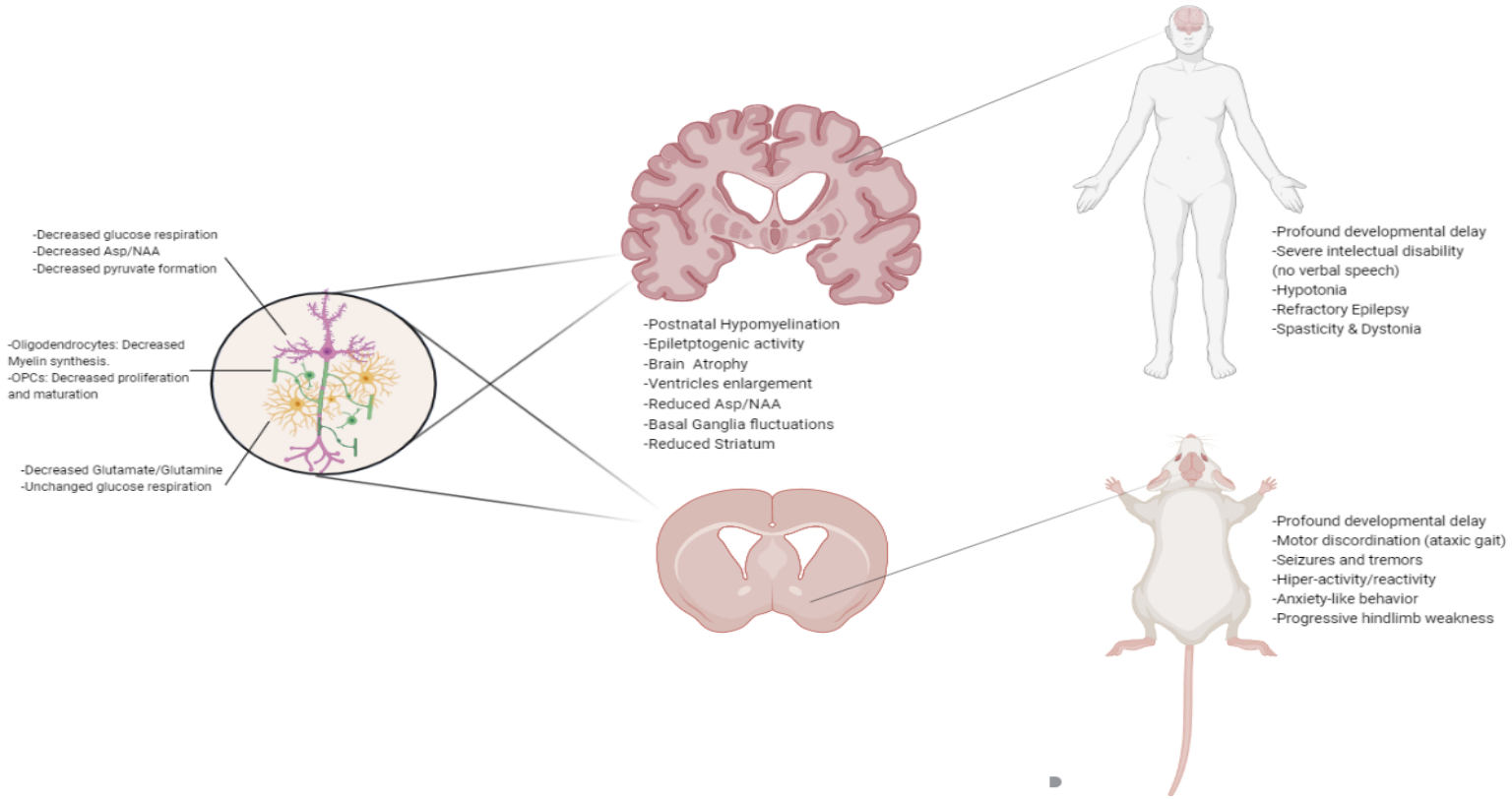


Dystonia-spasticity in a patient with a novel *SLC25A12* mutation

[1,2]Mered Parnes, MD, [3,4]Laurie Robak, MD, [2,3,4,5]Joshua M. Shulman, MD, PhD, [6]Amber Stocco, MD, [2]Joseph Jankovic, MD

[1]Section of Child Neurology and Developmental Neuroscience, Baylor College of Medicine, Texas Children's Hospital
[2]Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, TX
[3]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX
[4]Department of Neuroscience, Baylor College of Medicine, Houston, TX
[5]Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Houston, TX
[6]Pediatric Neurology, INTEGRIS Health, Oklahoma City

Effects of Aralar-MAS deficiency on brain cells, brain tissue and whole body



I. **To identify metabolic pathways bypassing the bioenergetic déficit and the pathological phenotype in Aralar-KO mice (and humans)**

Aralar/AGC1 deficiency: Early infantile epileptic encephalopathy 39

AGC1 Deficiency Associated with Global Cerebral Hypomyelination

Rolf Wibom, Ph.D., Francesco M. Lasorsa, Ph.D., Virpi Töhönen, Ph.D., Michela Barbaro, Ph.D., Fredrik H. Sterky, M.D., Thomas Kucinski, M.D., Ph.D., Karin Naess, M.D., Monica Jonsson, M.D., Ciro L. Pierri, Chem.D., Ferdinando Palmieri, M.D., and Anna Wedell, M.D., Ph.D.

N ENGL J MED 361;5 NEJM.ORG JULY 30, 2009

The ketogenic diet compensates for AGC1 deficiency and improves myelination

*†Maria Dahlin, ‡Daniel A. Martin, §Zandra Hedlund, ¶Monica Jonsson, **††Ulrika von Döbeln, and †††‡‡Anna Wedell

Epilepsia, 56(11):e176–e181, 2015
doi: 10.1111/epi.13193

Expanding Phenotypic Spectrum of Cerebral Aspartate–Glutamate Carrier Isoform 1 (AGC1) Deficiency

Brian Pfeiffer[1,2] Kuntal Sen[3] Shagun Kaur[1,2] Kara Pappas[2,4,5]

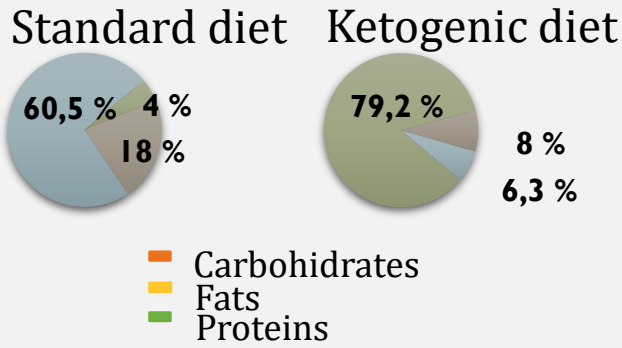
Neuropediatrics October 6, 2019

Ketogenic diet (KD) : Partial recuperation

- Voluntary movement ↑
- Psichomotor development
- Epilepsy ↓
- Ventricle size ↓
- Myelination ↑

Ketogenic diet (KD):

Reduction in carbohydrate intake in favor of fatty acid intake



The ketogenic diet: metabolic influences on brain excitability and epilepsy

Andrew Lutas and Gary Yellen

Department of Neurobiology, Harvard Medical School, Boston, MA 02115, USA

CUERPOS CETÓNICOS >>> GLUCOSA

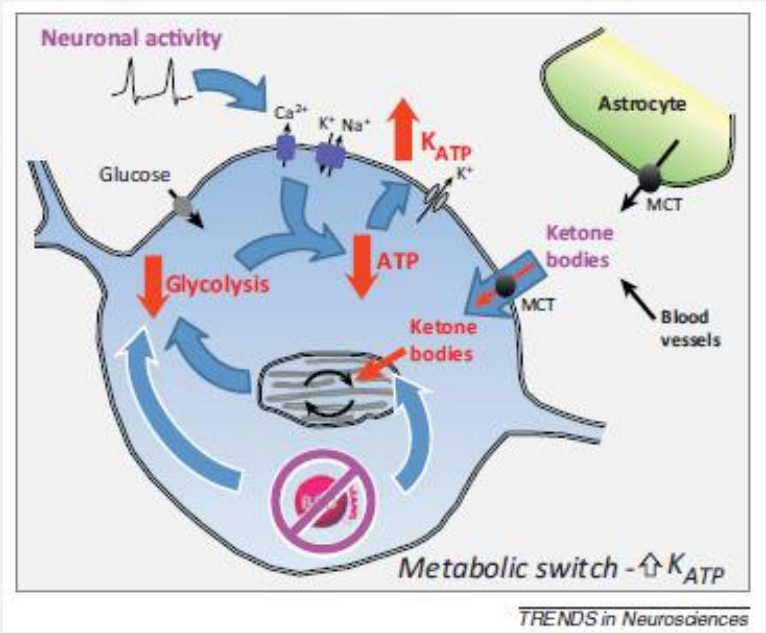
↑ Metabolismo mitocondrial >> Glucólisis ↓
ATP mitocondrial >> ATP glicolítico

↓

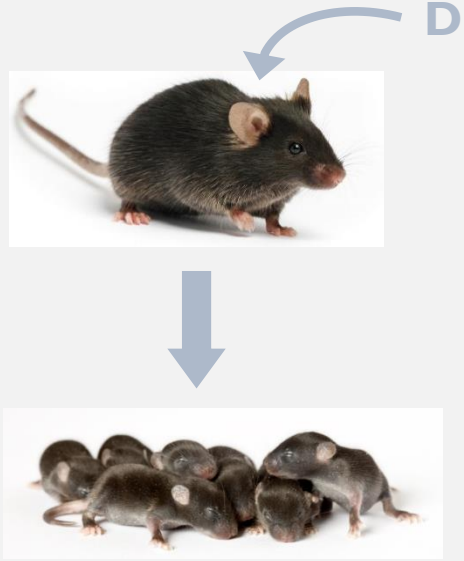
Activación K_{ATP} channels
Hiperpolarización celular

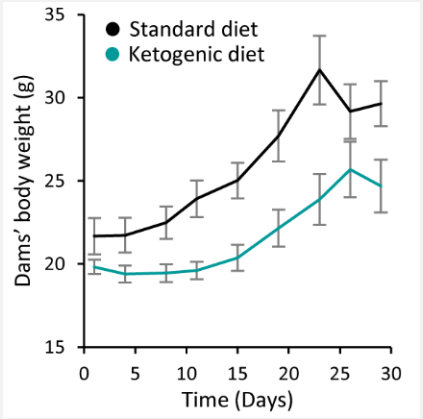
↓

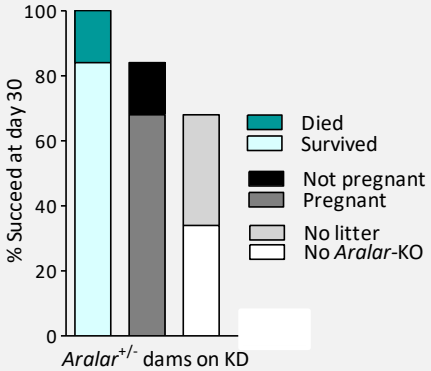
↓ Excitabilidad neuronal



Ketogenic diet had negative effects on pregnant Aralar$^{+/-}$ mice



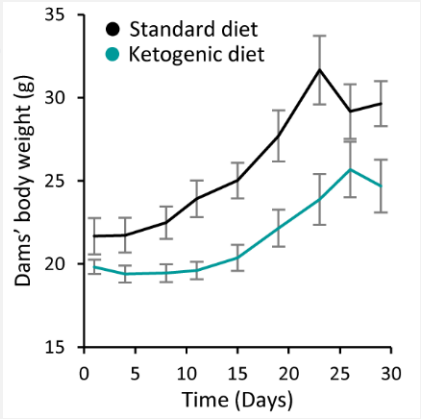


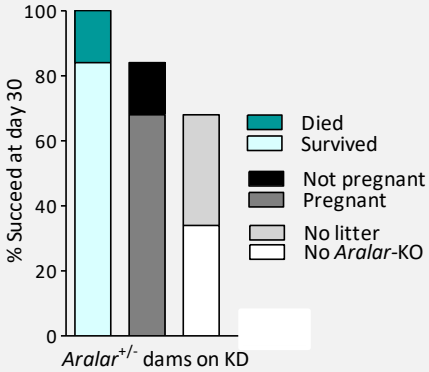


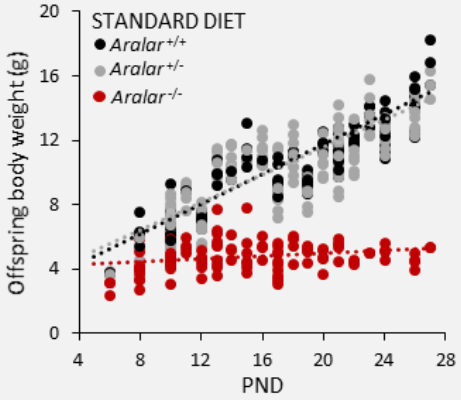
Ketogenic diet had negative effects on pregnant Aralar$^{+/-}$ mice
And affected the survival of the offspring

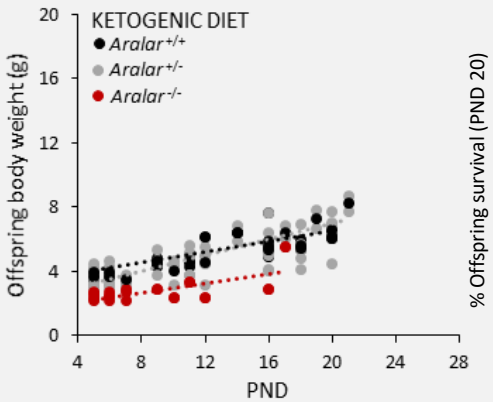
Dieta

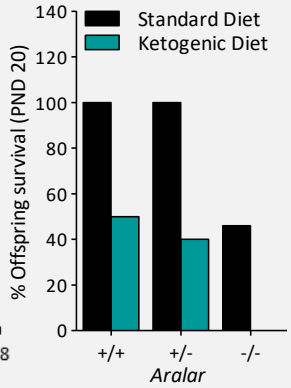
PND 5



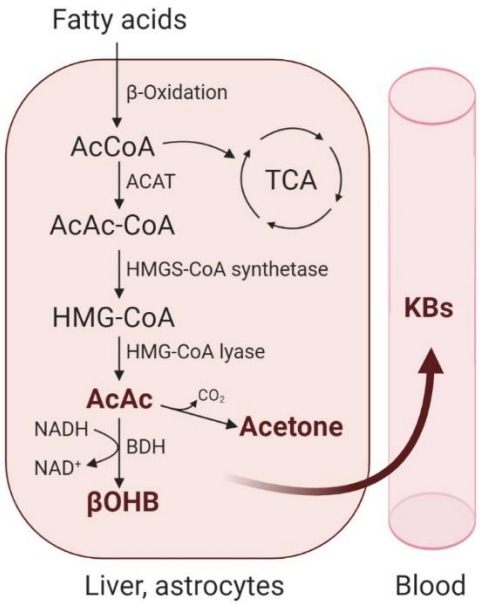




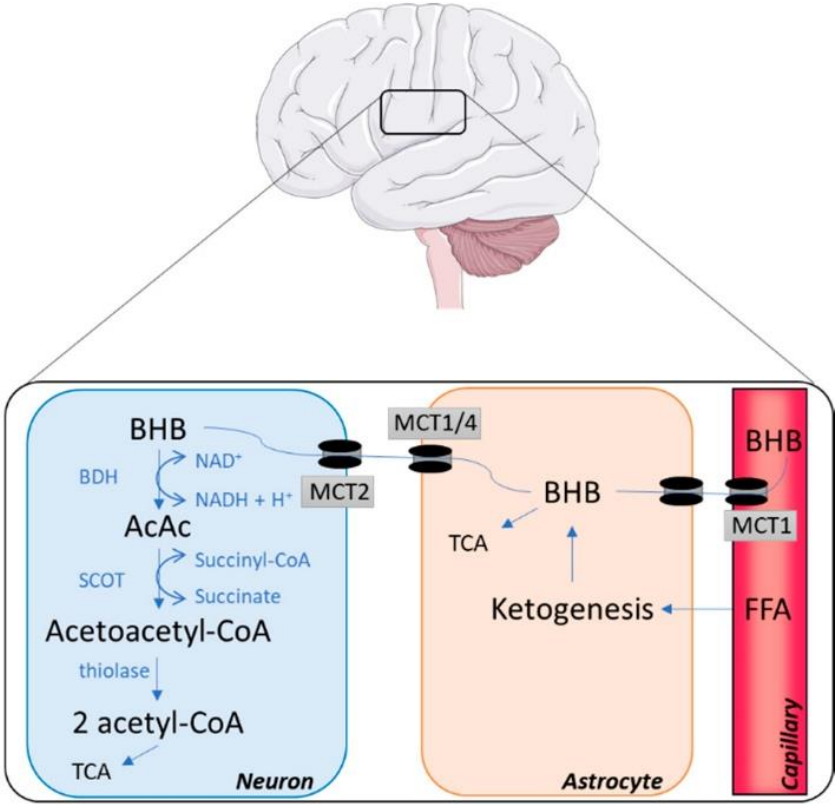




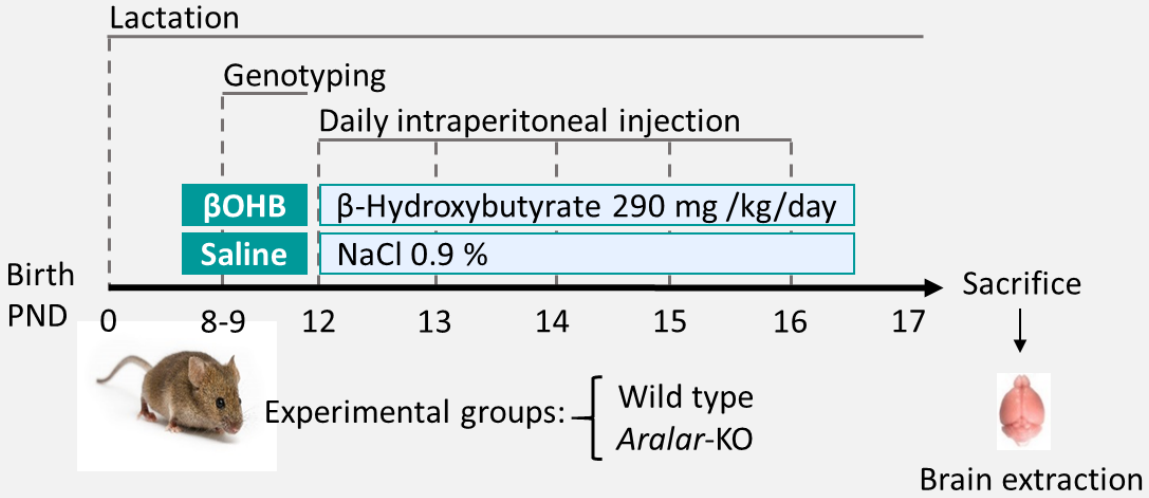
Excess fatty acids induce liver ketogenesis



Ketone bodies are an alternative energy source to carbohydrates in brain



Intraperitoneal injections of β-Hydroxybutyrate in Aralar-KO mice

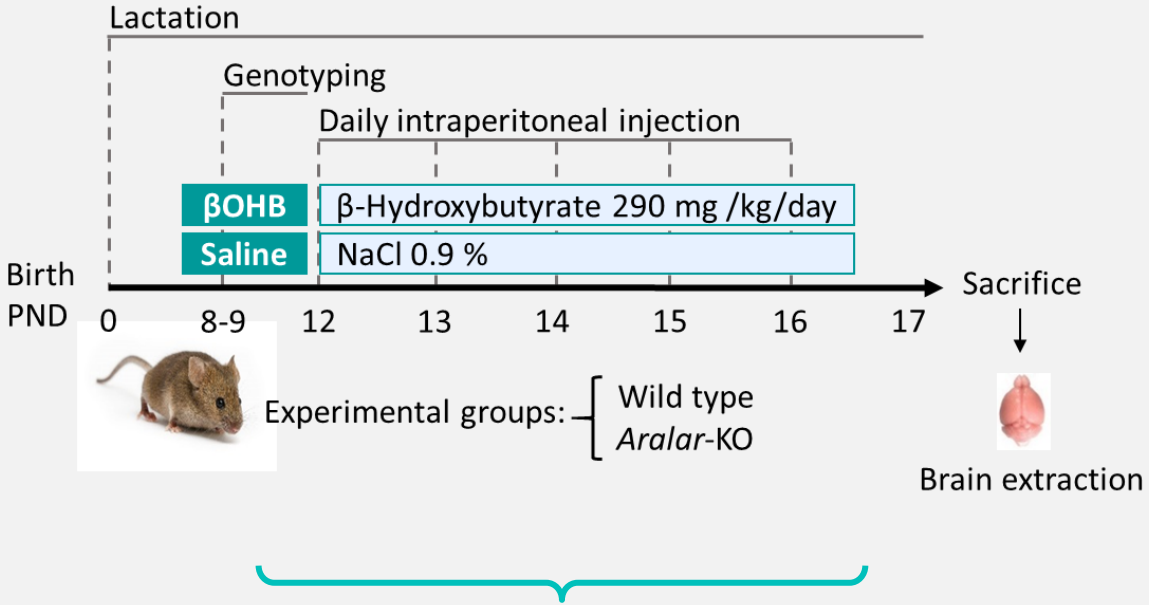


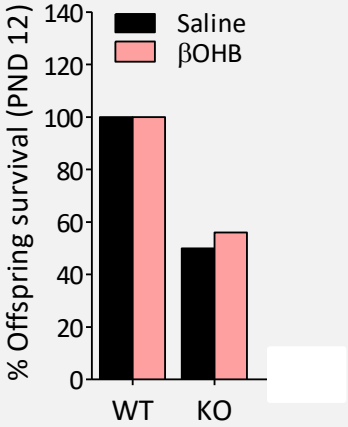
Phenotype

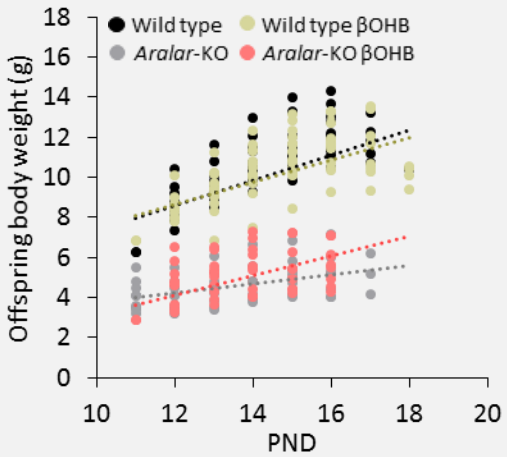
BIOCHEMICAL ANALYSIS

1) **DOPAMINERGIC METABOLISM**
2) **MYELINIZATION**

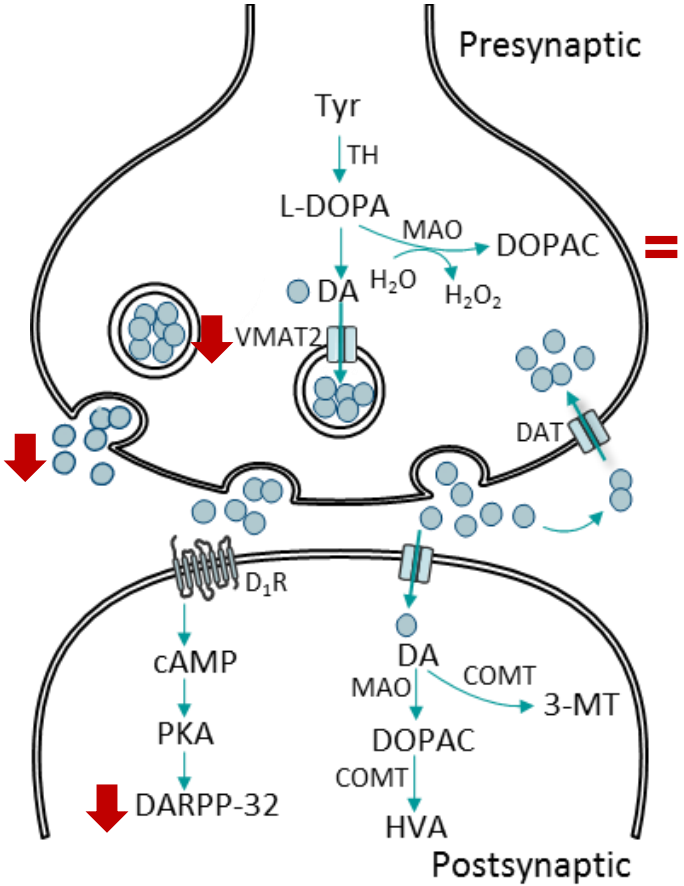
βOHB *in vivo* does not modify the lifespan or the weight of Aralar-KO mice

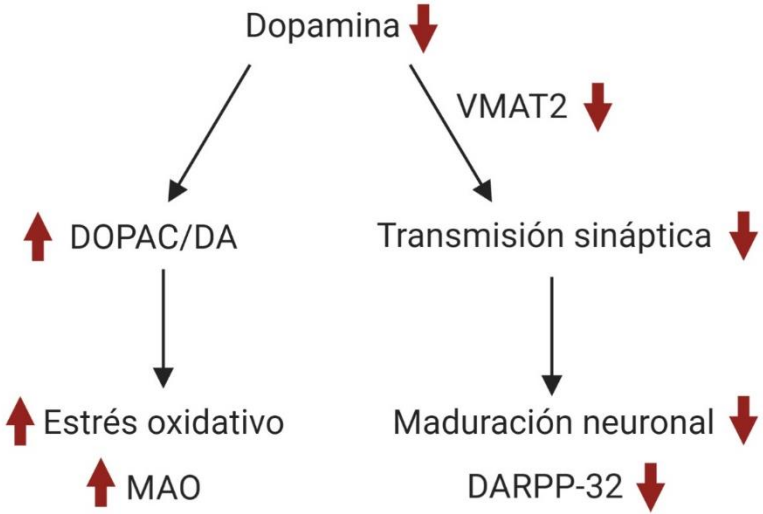






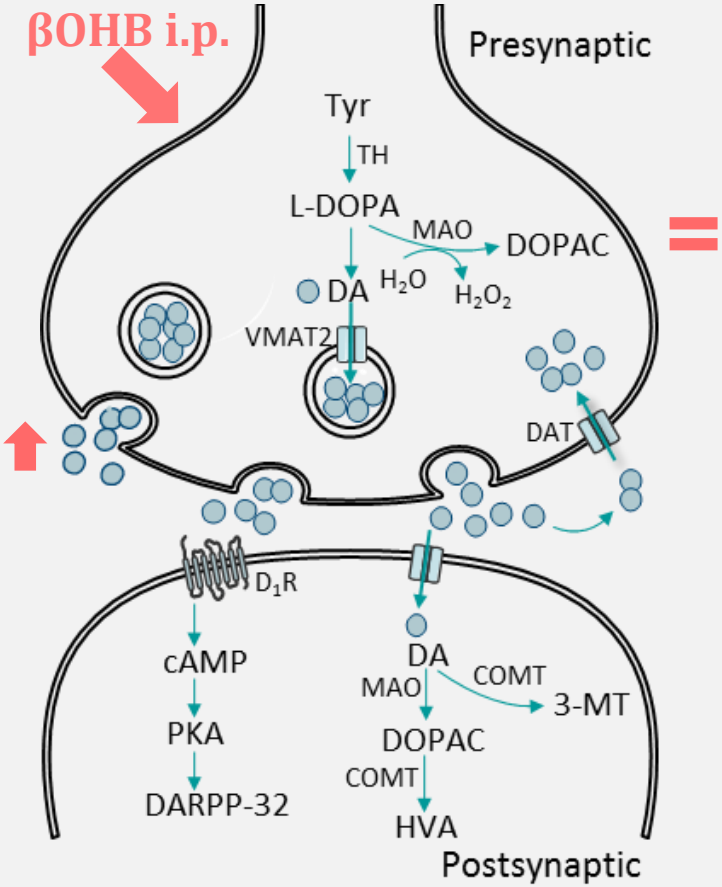
Aralar deficiency alters striatal dopamine metabolism

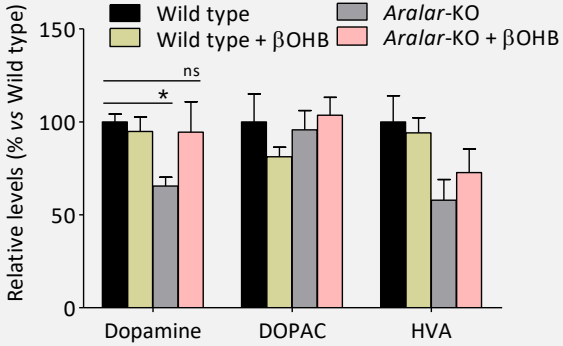


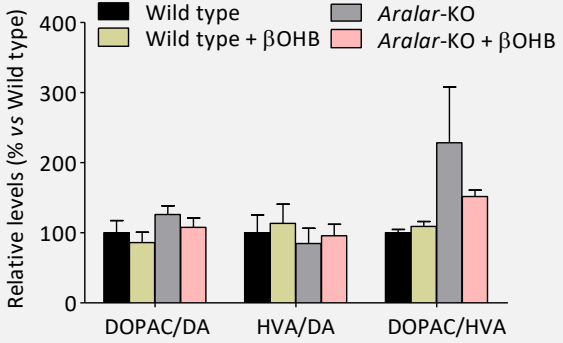


Llorente-Folch *et al.*, (J. Neurochem, 2013)

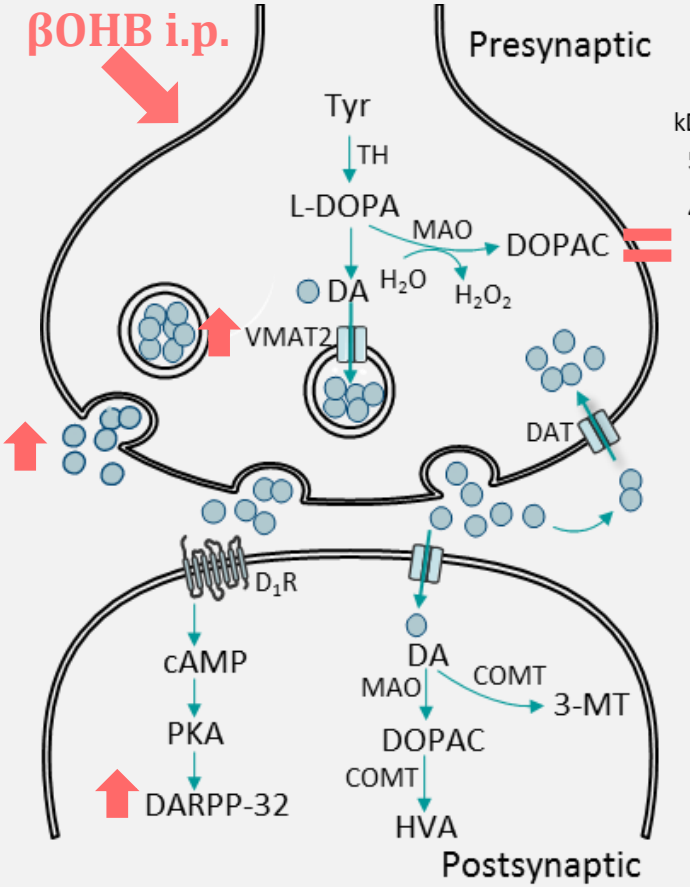
βOHB partially reverses the alteration of dopamine metabolism and signaling in the striatum of Aralar-KO mice

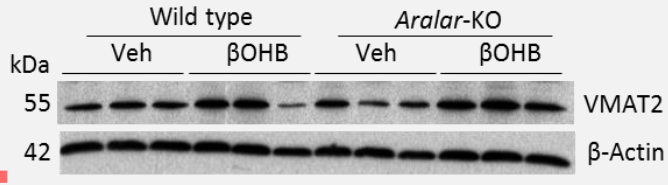


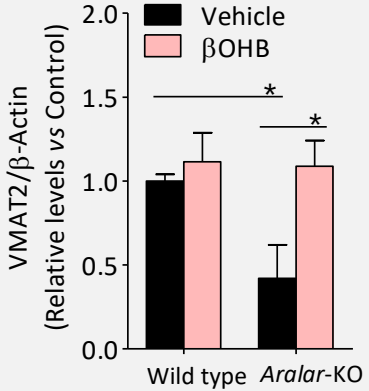


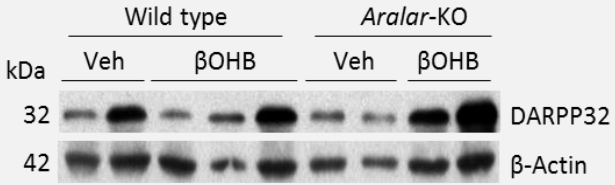


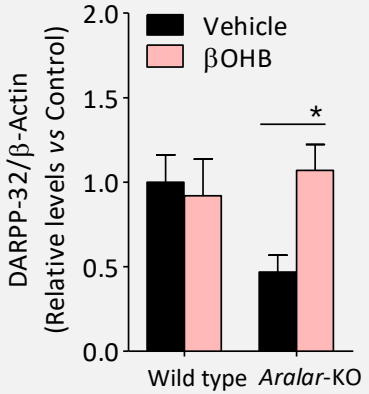
βOHB partially reverses the alteration of dopamine metabolism and signaling in the striatum of Aralar-KO mice



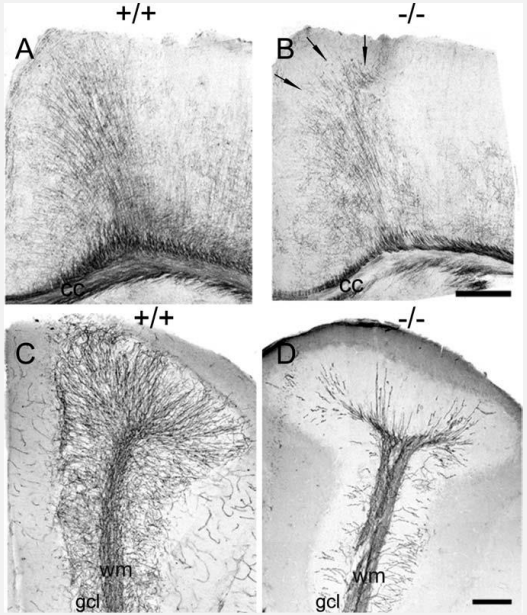




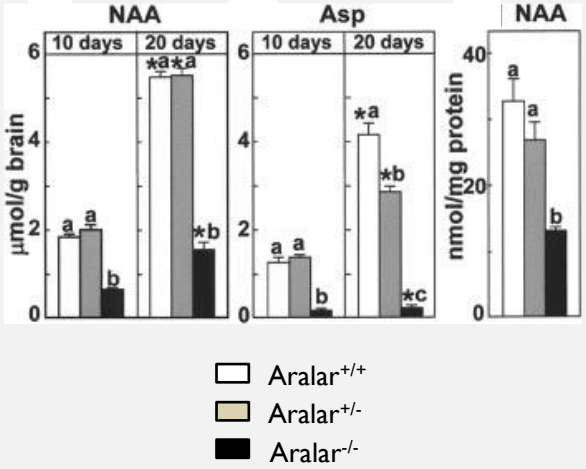




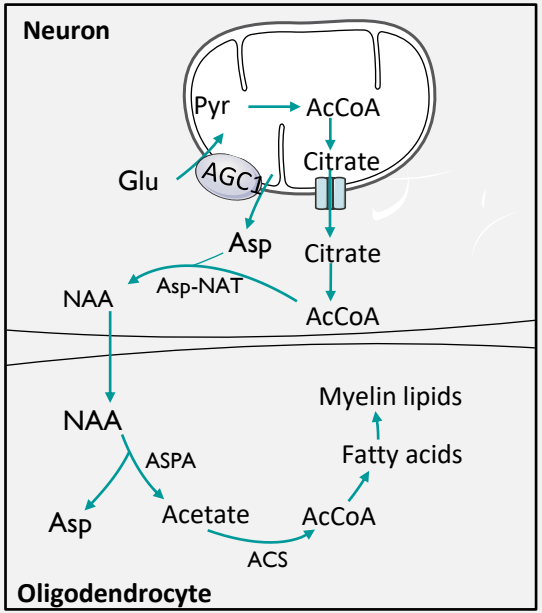
Aralar deficiency causes postnatal hypomyelination



Ramos *et al., J. Biol. Chem,* (2011)

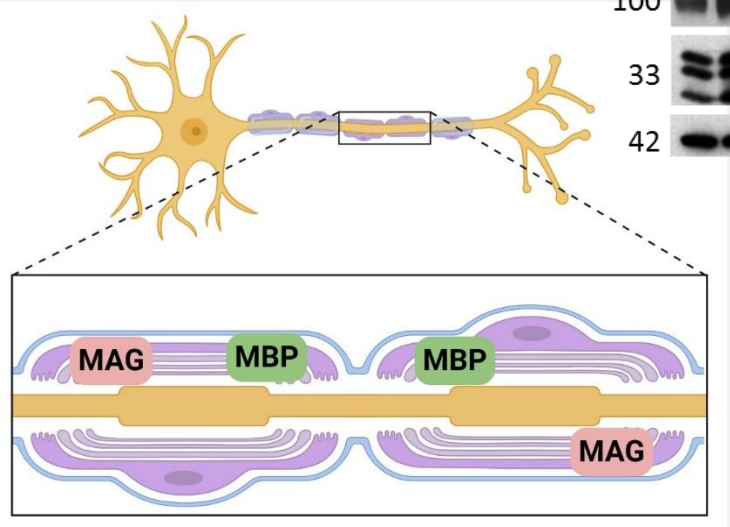


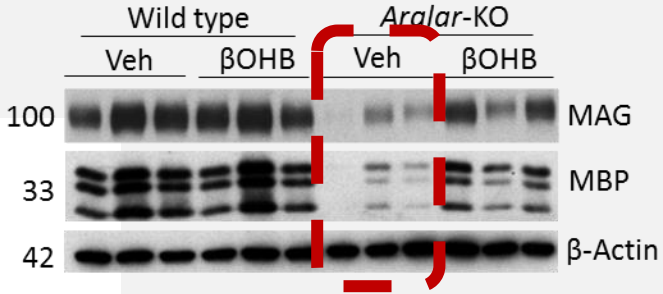
Jalil *et al., J. Biol. Chem* (2005)

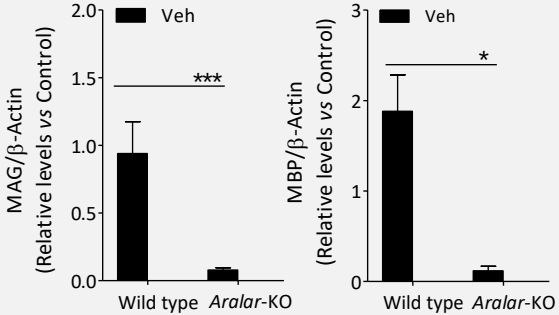


Satrústegui *et al., Physiol Rev,* (2007)

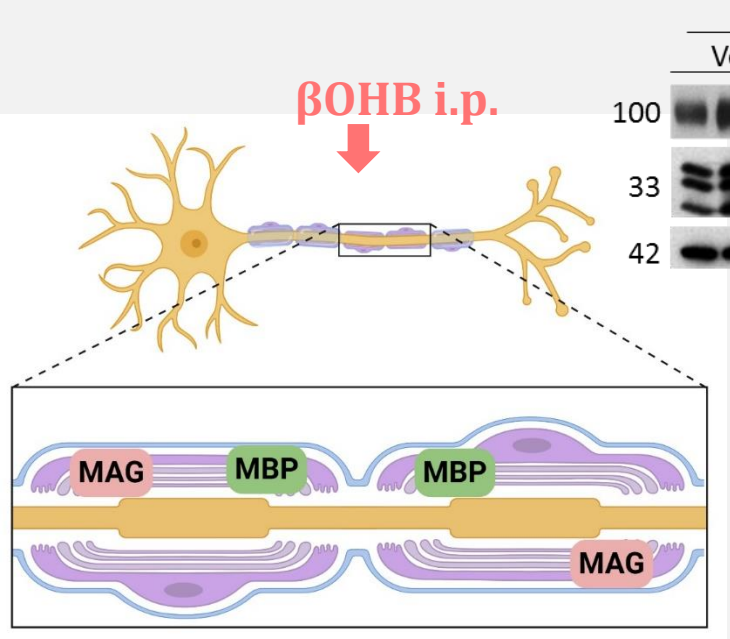
Aralar deficiency causes postnatal hypomyelination

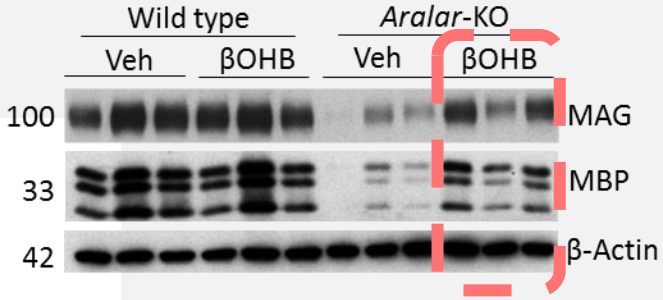


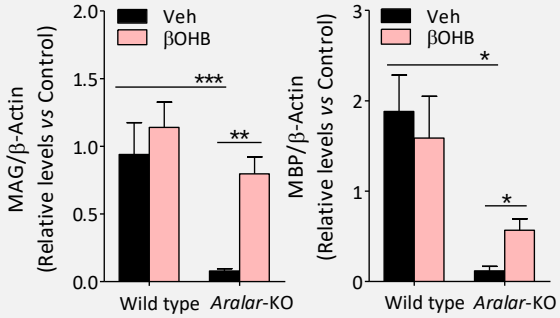




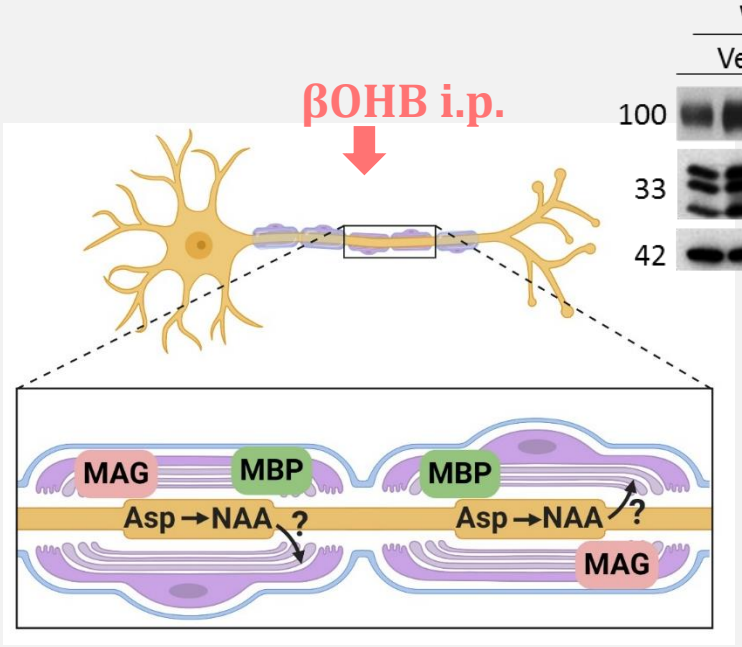
βOHB recovers cortical myelination

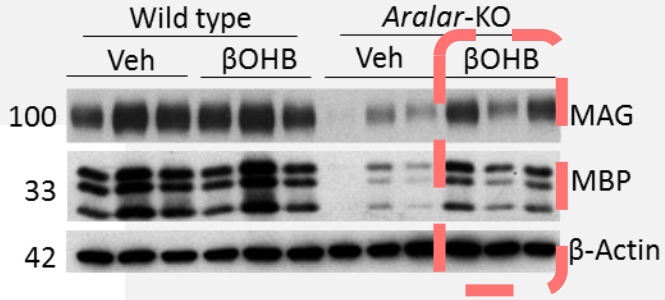


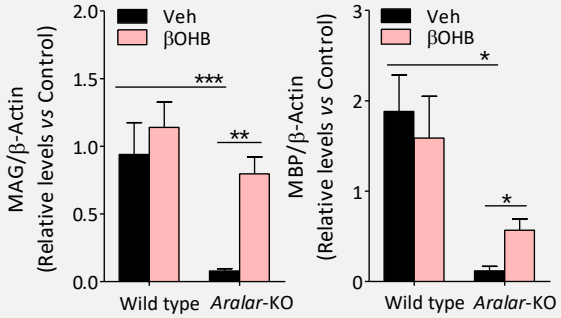


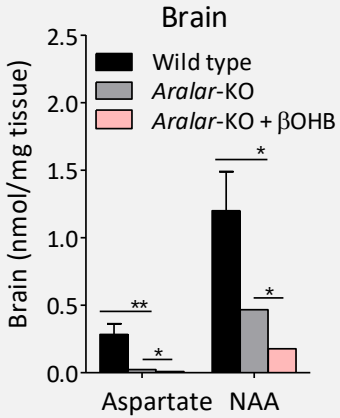


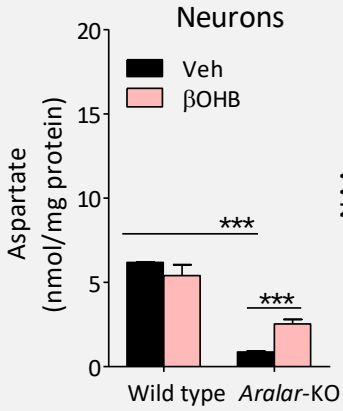
βOHB recovers cortical myelination and the neuronal synthesis of aspartate and NAA in Aralar deficiency

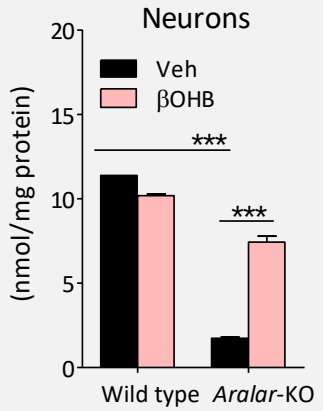




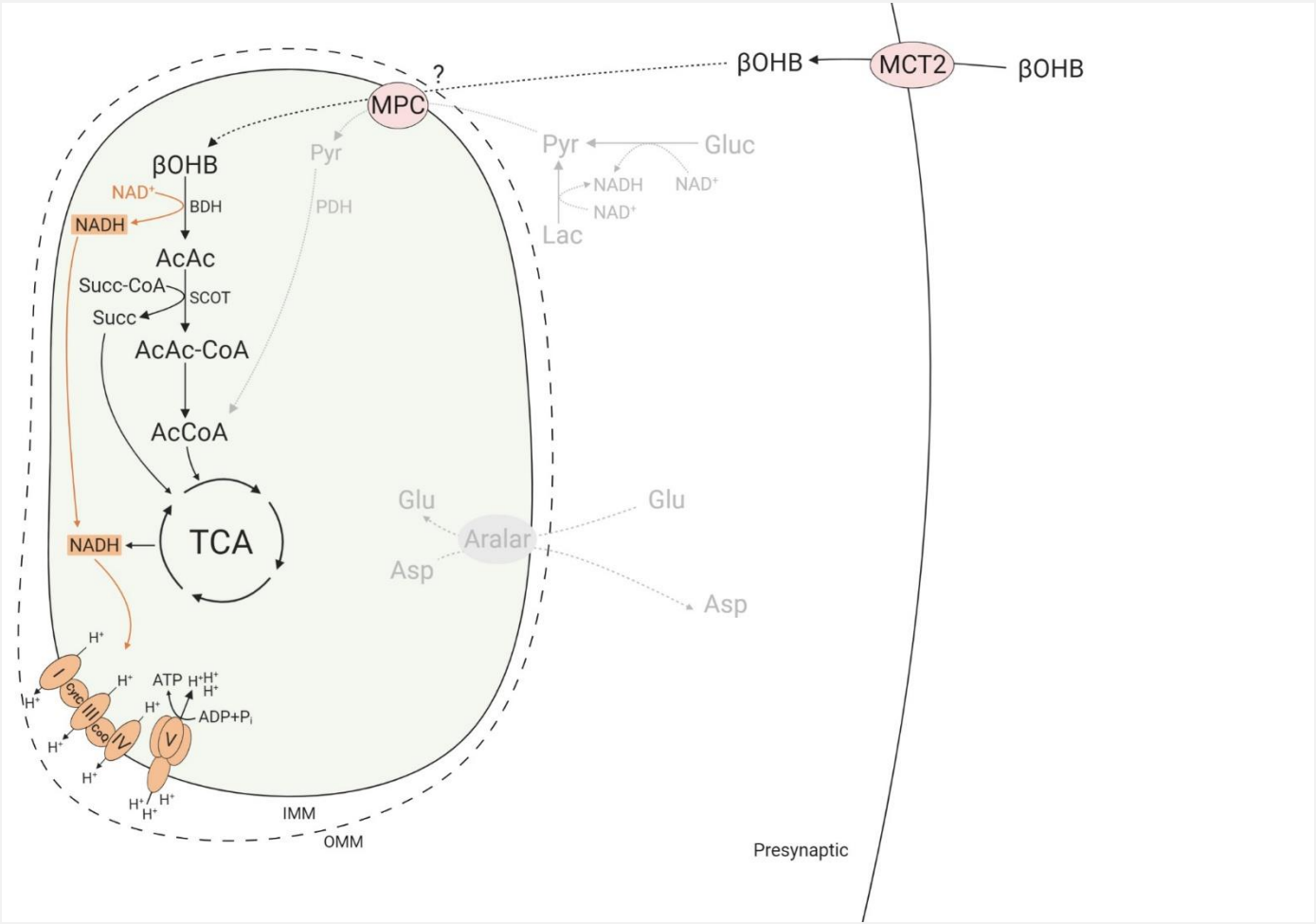




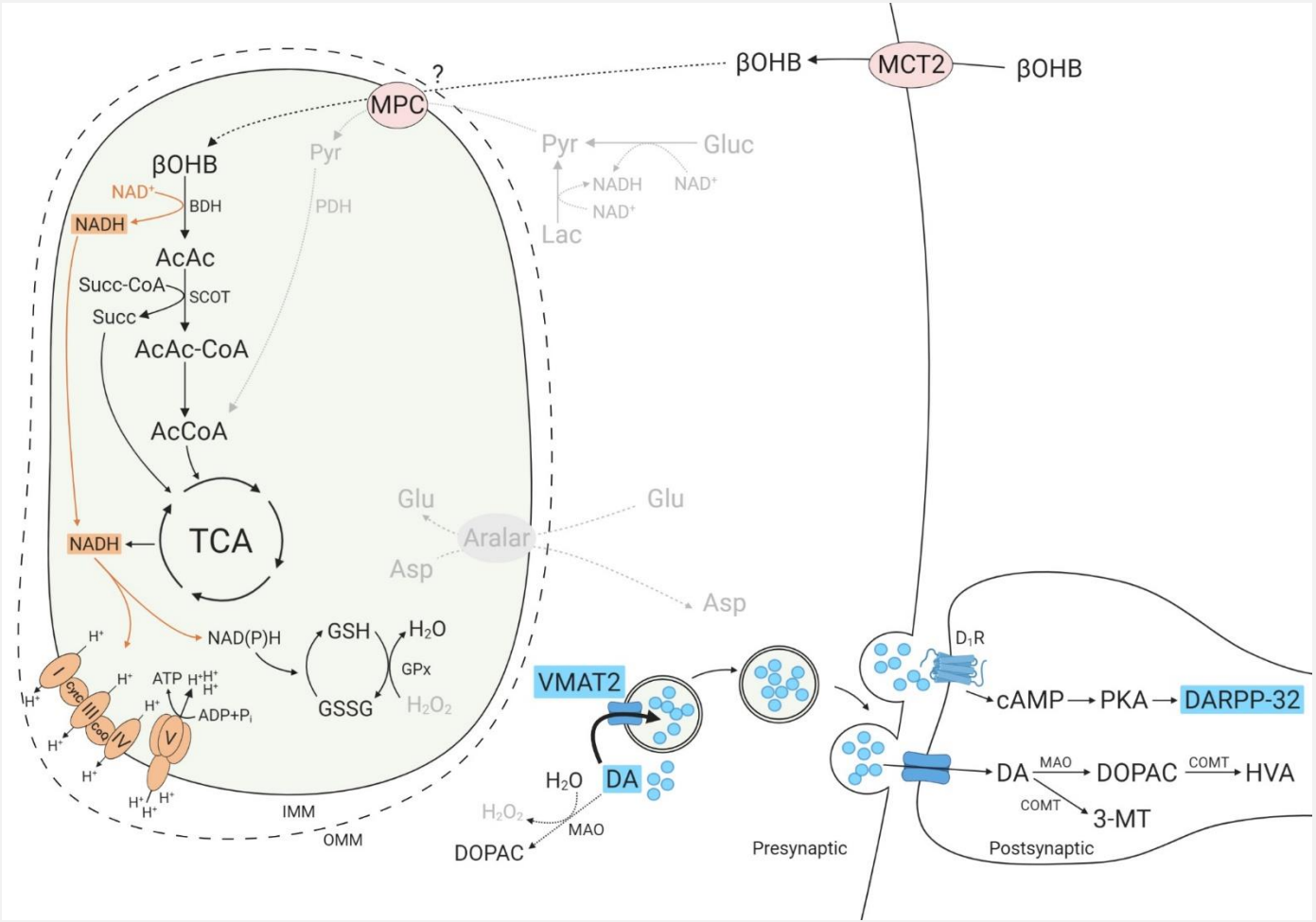




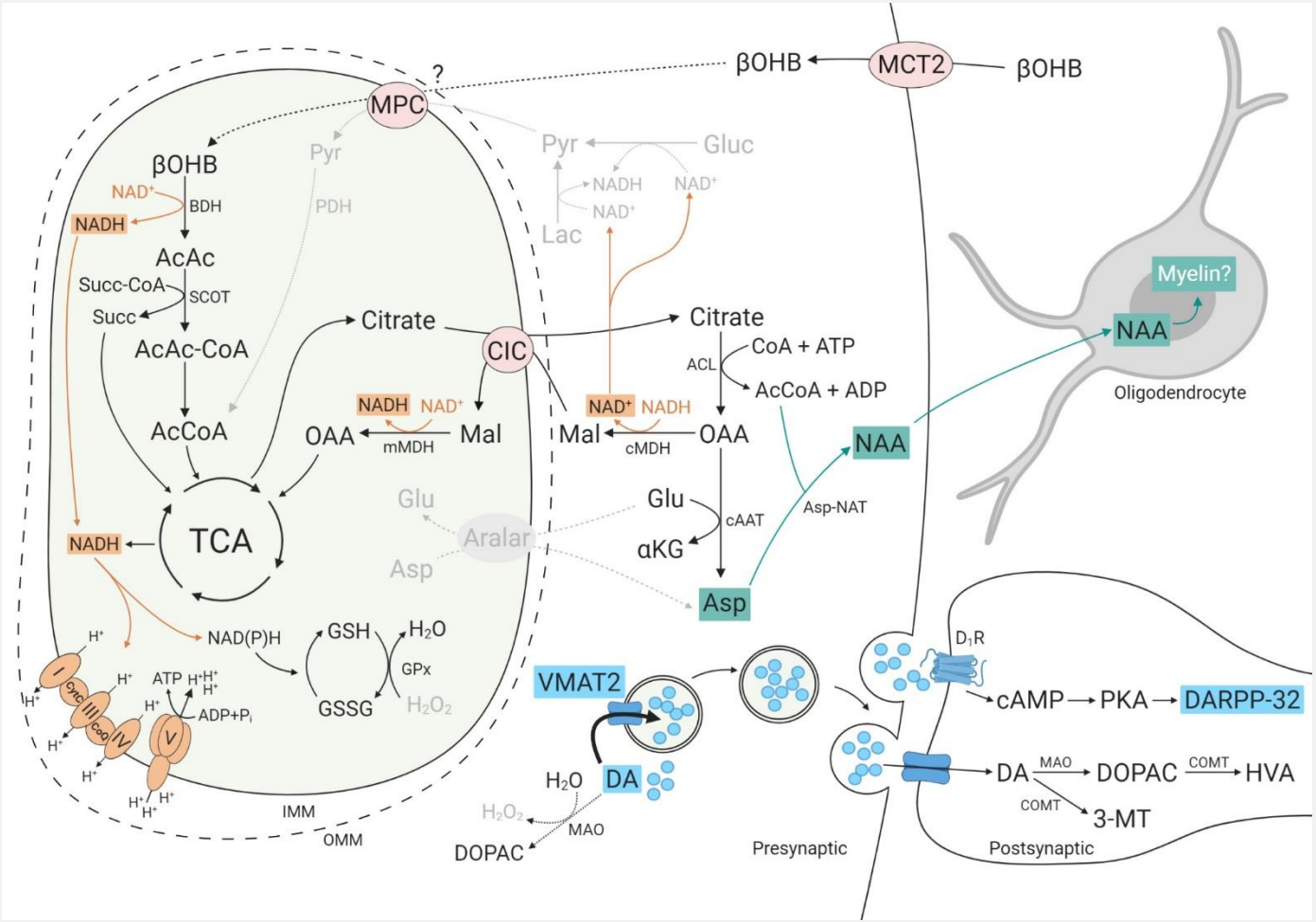
βOHB bypasses Aralar deficiency



βOHB bypasses Aralar deficiency



βOHB bypasses Aralar deficiency



COLABORACIÓN

- *Oferta/Demanda: y este es el punto importante. El objetivo es:*

1. *Exponer al resto de los investigadores aquellas habilidades o tareas de las que te puedes considerar experto:*

   Modelos animales modificados genéticamente, función mitocondrial, imaging *in vivo* por FRET..

2. *Demandar ayuda al resto de investigadores en alguna tarea en la que quieras profundizar y en la que no seas experto (técnicas, equipos….)*

ÁREA: NEUROCIENCIAS

Comunidad de Madrid

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

Francesc Palau
Takeyori Saheki
Ferdinando Palmieri
Paola Bovolenta
Sebastián Cerdán
Claes Wollheim
Michael Duchen
Gyorgy Szabadkai
Jim Hurley
Eduardo Rial
Aranzazu Sanchez
Oscar Herreras
María José Casarejos

mtdlab

IIS FJD
INSTITUTO DE INVESTIGACIÓN SANITARIA
FUNDACIÓN JIMÉNEZ DÍAZ

III REUNIÓN ANUAL DEL ÁREA DE NEUROCIENCIAS DEL IIS-FJD
8 de junio del 2021

UAM Universidad Autónoma de Madrid

Hospital Universitario Fundación Jiménez Díaz
Grupo quirónsalud

IIS FJD
INSTITUTO DE INVESTIGACIÓN SANITARIA
FUNDACIÓN JIMÉNEZ DÍAZ