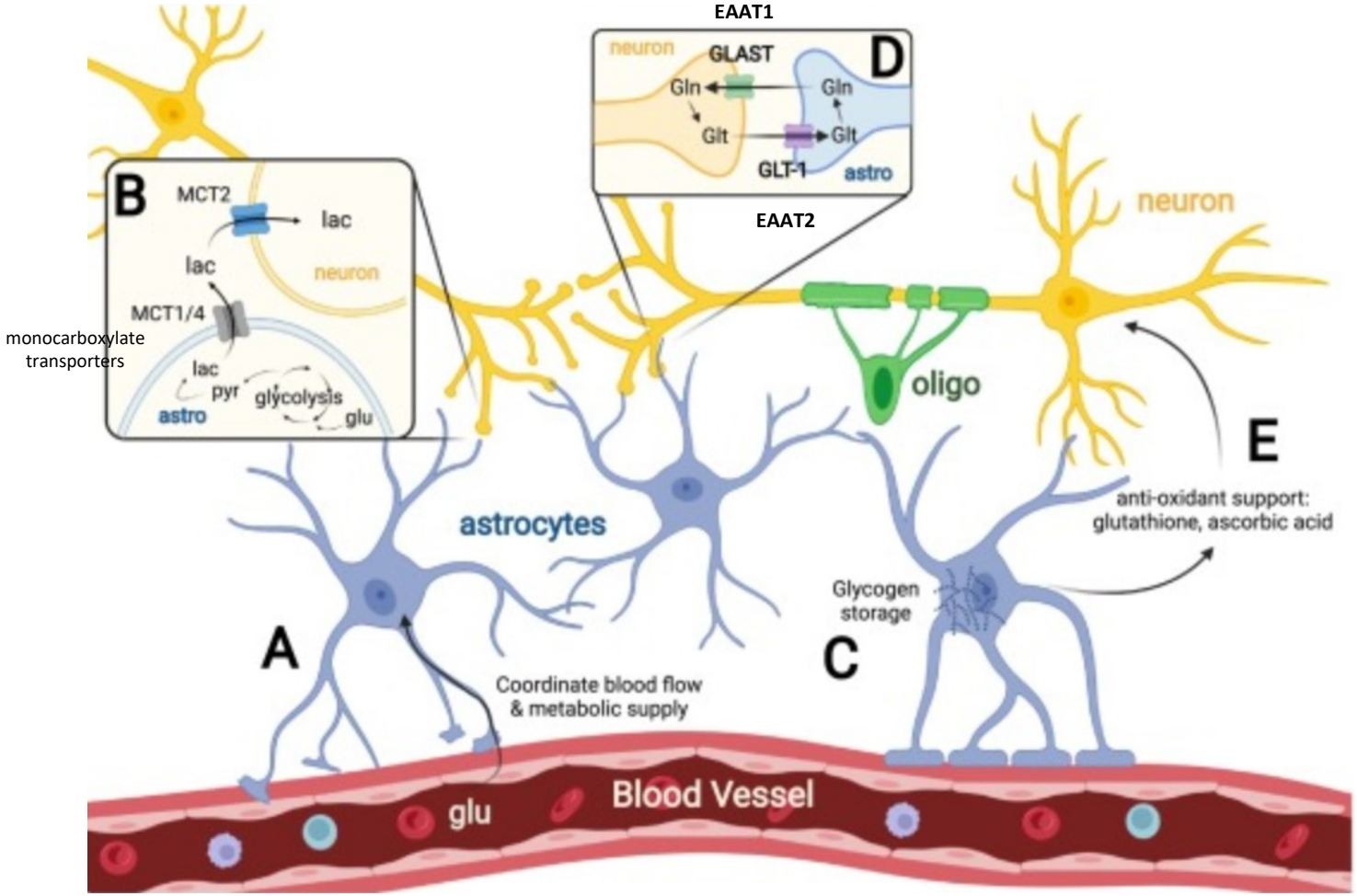
Cross-talk fra neuroni e cellule della mielina:

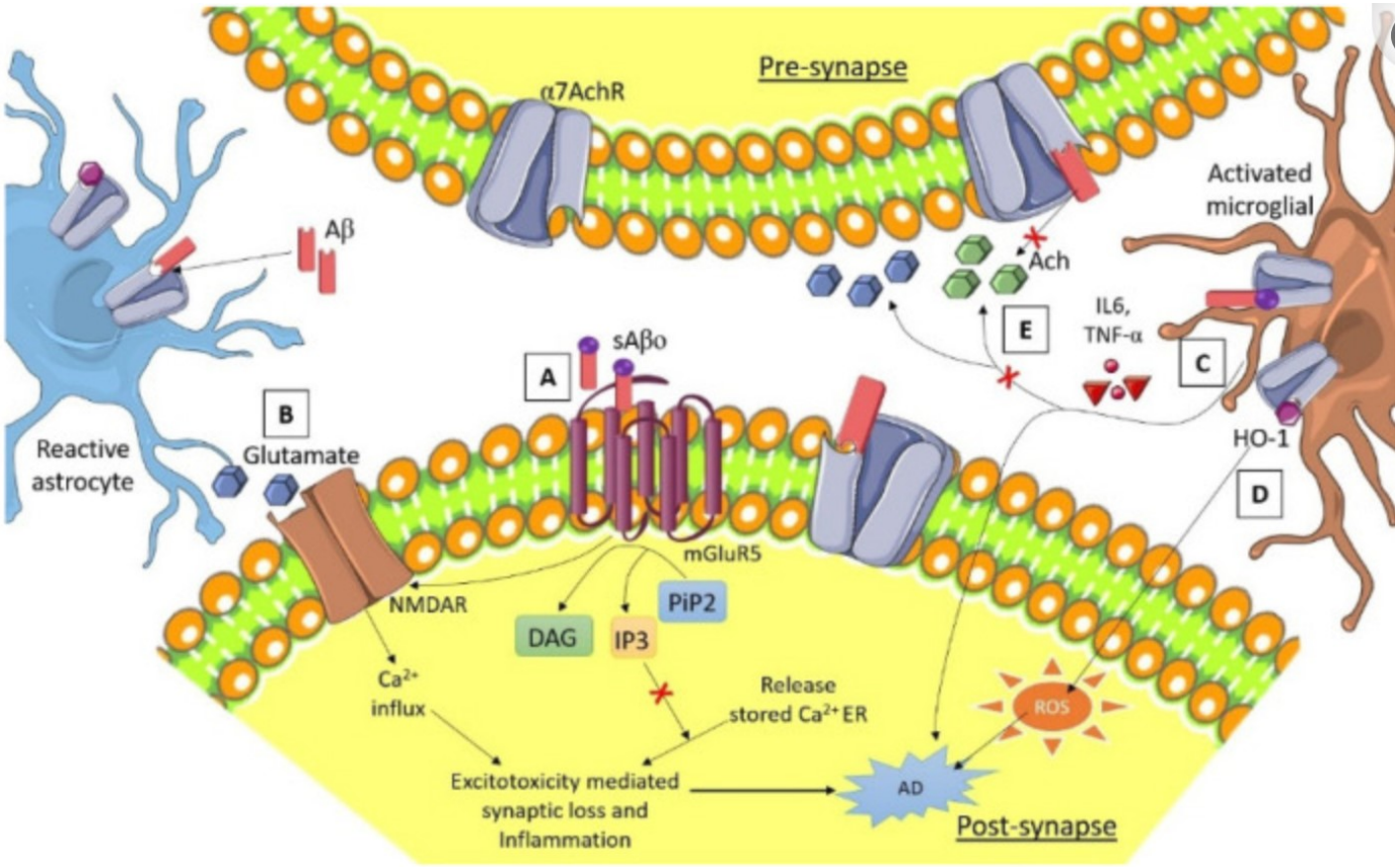
neurotrasmissione o gliotrasmissione ?

Valerio MAGNAGHI, PhD
Dept. of Pharmacological and Biomolecular Sciences «R. Paoletti»
University of Milan, Italy



Neurobiology of Disease 2022
https://doi.org/10.1016/j.nbd.2022.105766

neuron-astrocyte-microglia cross-talk and calcium homeostasis …..*pathological implications*



Chavda et al. Brain Sci. 2022 Jan; 12(1): 75

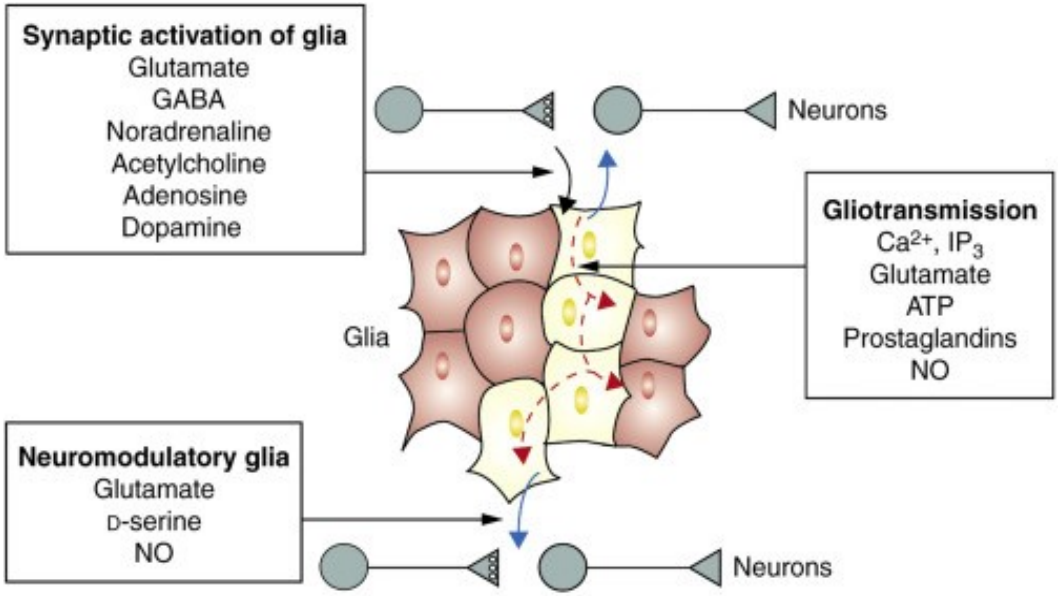
DOI 10.1007/s00702-004-0119-x
J Neural Transm (2005) 112: 121–125

Journal of Neural Transmission
Printed in Austria

Roles for gliotransmission in the nervous system

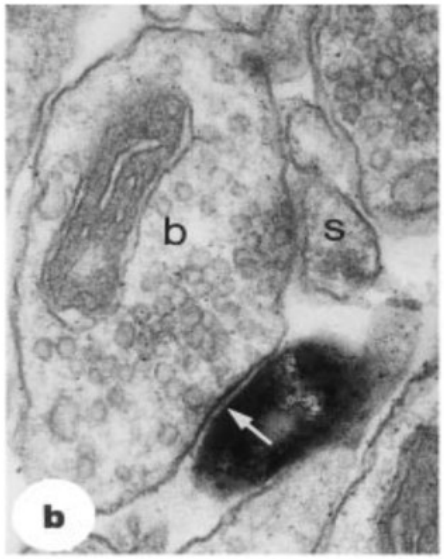
Q. Zhang and **P. G. Haydon**

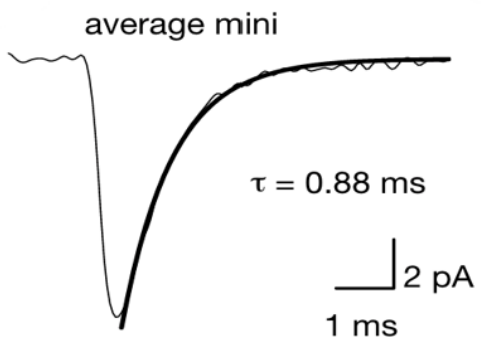
Department of Neuroscience, School of Medicine, University of Pennsylvania, Philadelphia, PA, USA



Current Opinion in Neurobiology
https://doi.org/10.1016/B978-0-12-802401-0.00003-X

Neurons make synaptic connections with OPCs



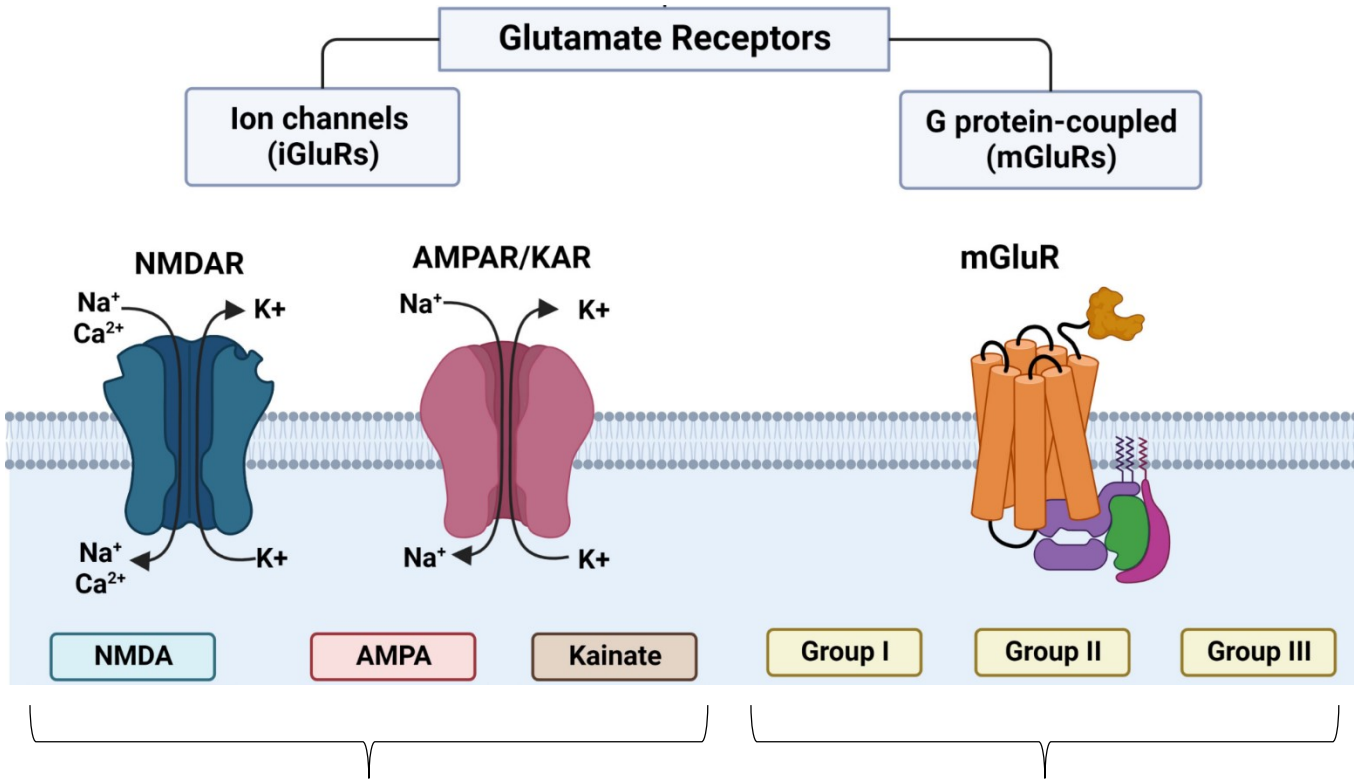


Bergles et al. *Nature* 2000

Neuron-OPC synapses (GLUTergic but also GABAergic) exist in both white matter and grey matters

Bergles et al. *Nature* 2000
Lin et al. *Nat Neurosci* 2004
Lin et al. *Neuron* 2005
Jabs et al. *J Cell Sci* 2005
Ge et al. *Science* 2006
Kukley et al. *Nat Neurosci* 2007
Zinski et al. *Nat Neurosci* 2007
Karadottir et al. *Nat Neurosci* 2008
Velez-Fort et al. *J Neurosci* 2010

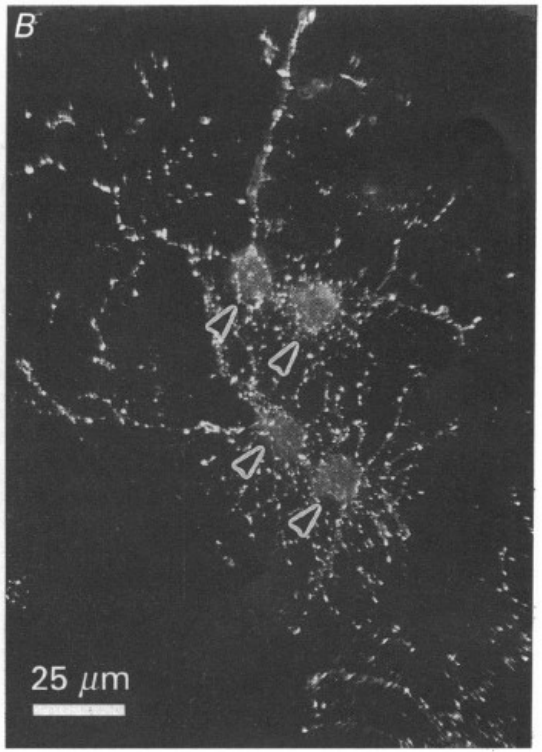
Glutamate receptors are important for synaptic transmission



García-Gaytán et al, Frontiers Endocrinol, 2022

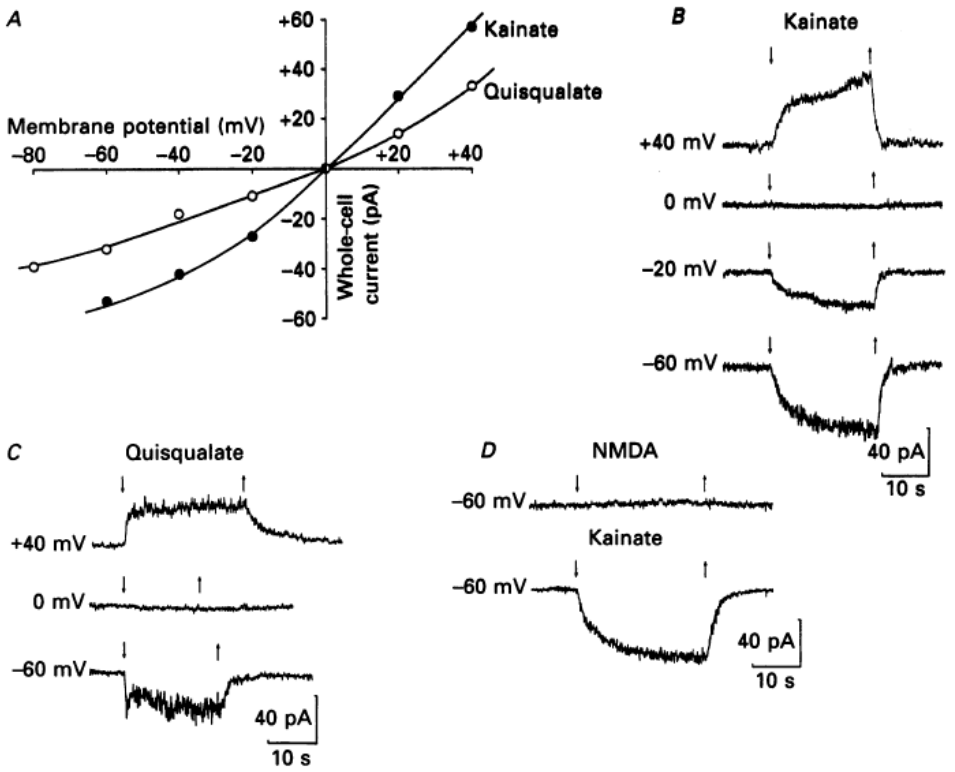
Functional glutamate receptors in oligodendrocytes

O2-A progenitor cells



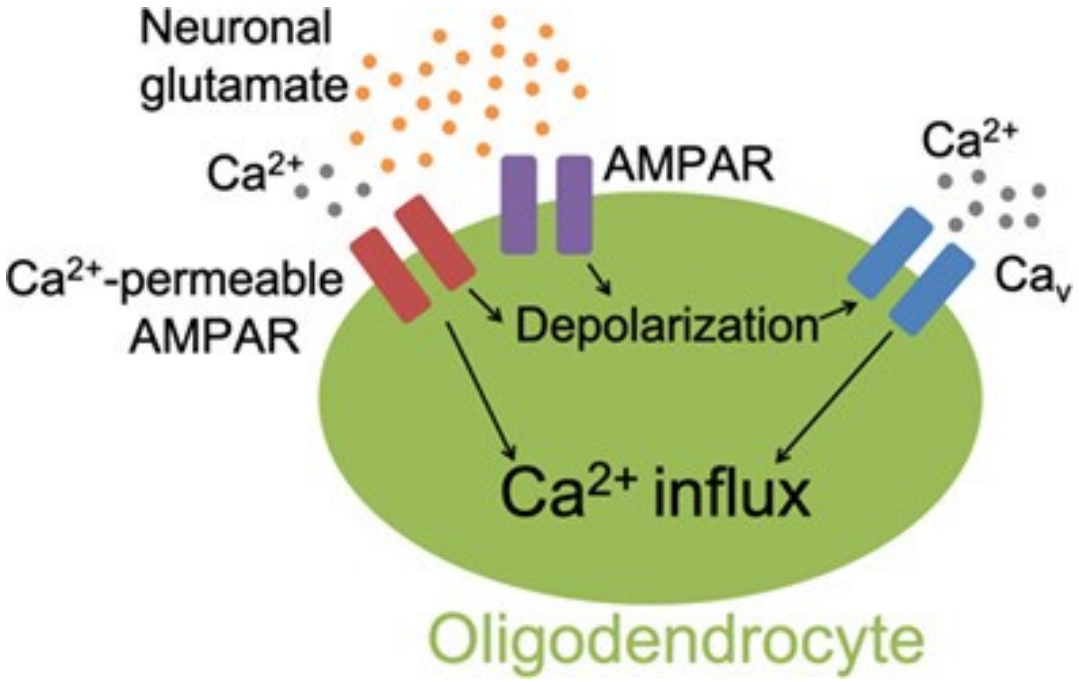
1-day old rat cerebellar culture

Currents mediated by AMPA/kainate receptors



Wyllie *et al, J Physiol, 1991*

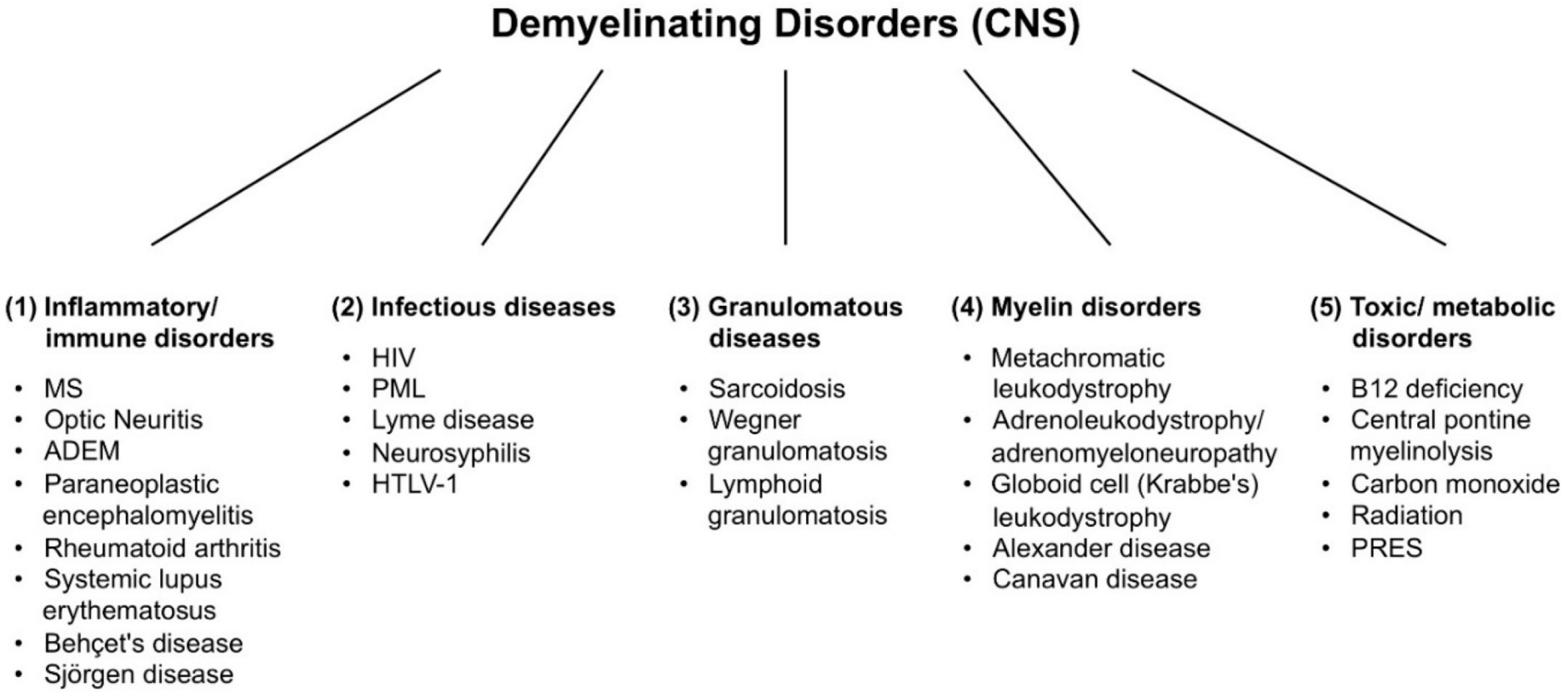
What is the function of glutamate receptors in OLIGO cells?



dominating concept for many years:

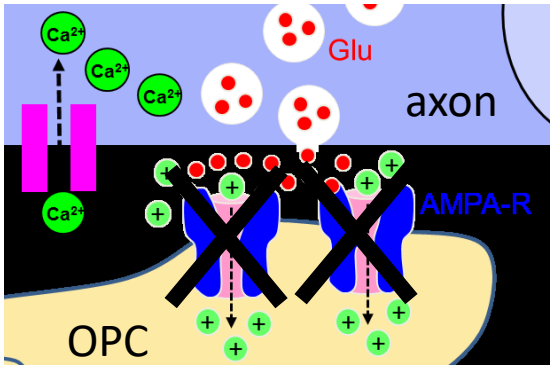
GLUT receptors mediate damage of OLIGO during diseases

Damage to oligodendrocytes mediates/triggers/accompanies many diseases

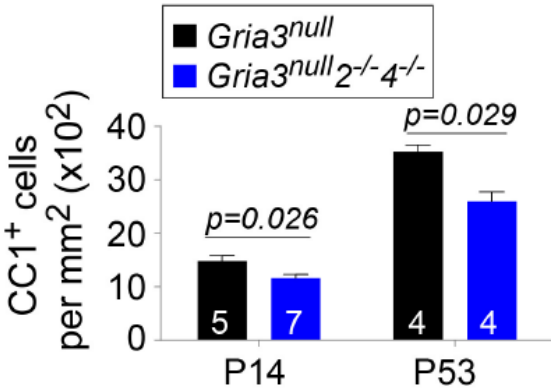


KO of GluA2, GluA3, GluA4 subunits of AMPARs in OPCs *in vivo* results in loss of oligodendrocytes

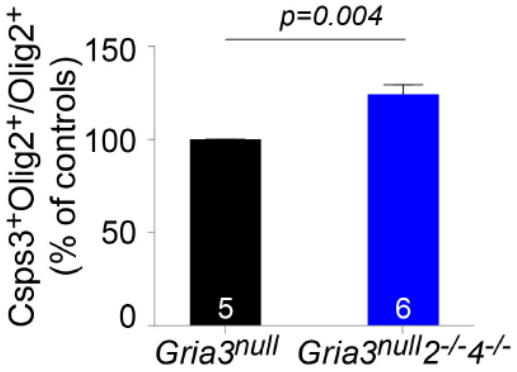
AMPAR KO



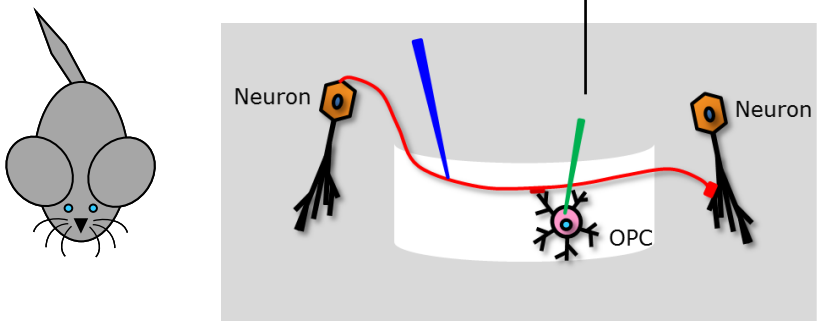
Reduced number of oligodendrocytes



Increased number of **apoptotic** oligodendrocyte lineage cells



No synaptic currents



Kougioumtzidou et al, Elife, 2017

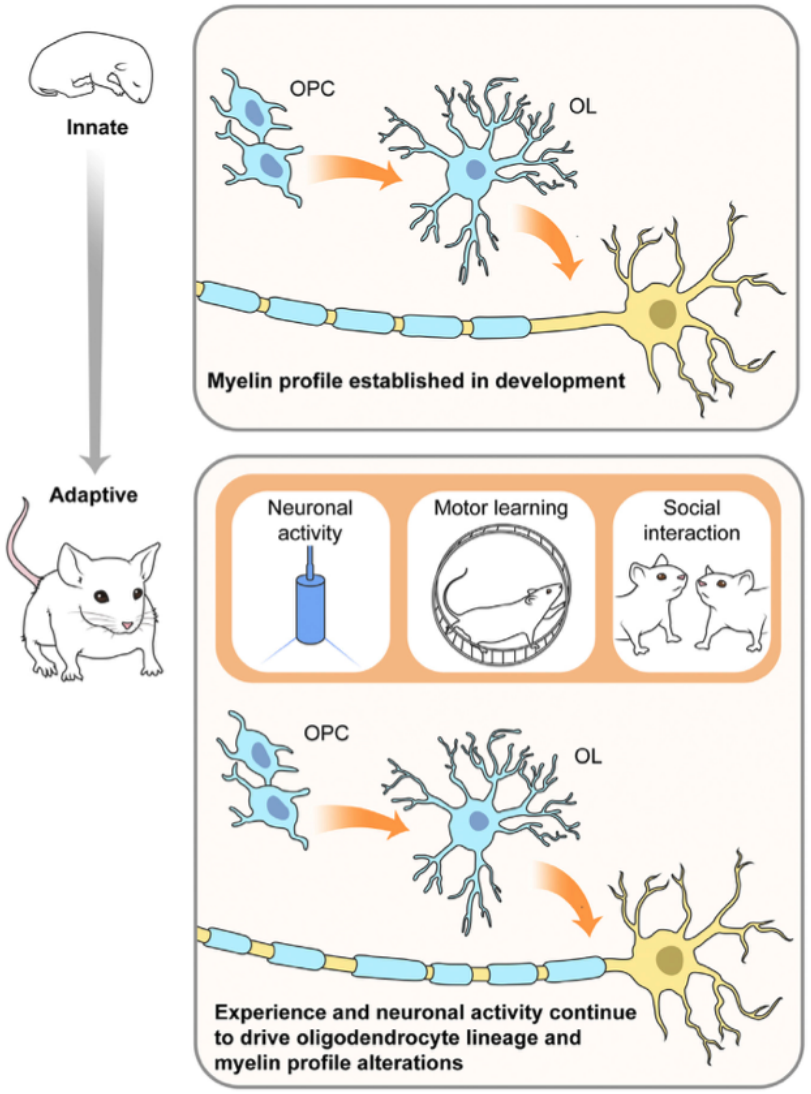
SUMMARY of GLUTAMATE and AMPAr in OLIGO

- Regulate balance proliferation/differentiation of OPCs in developing and adult brain
- Regulate survival of oligodendrocytes
- Contribute to damage of oligodendrocytes and axons

…….role in CNS myelination???

hypothesis of Activity-Dependent Myelination in the CNS

- An intrinsic and innate program can initial myelination
- Through the lifespan myelin remodeling in the CNS is a dynamic process, modulated by learning and social interaction
- Neuronal activity induces myelin remodeling



Mont and Monje 2017, Neuron

eLIFE elifesciences.org

RESEARCH ARTICLE

NG2 glial cells integrate synaptic input in global and dendritic calcium signals

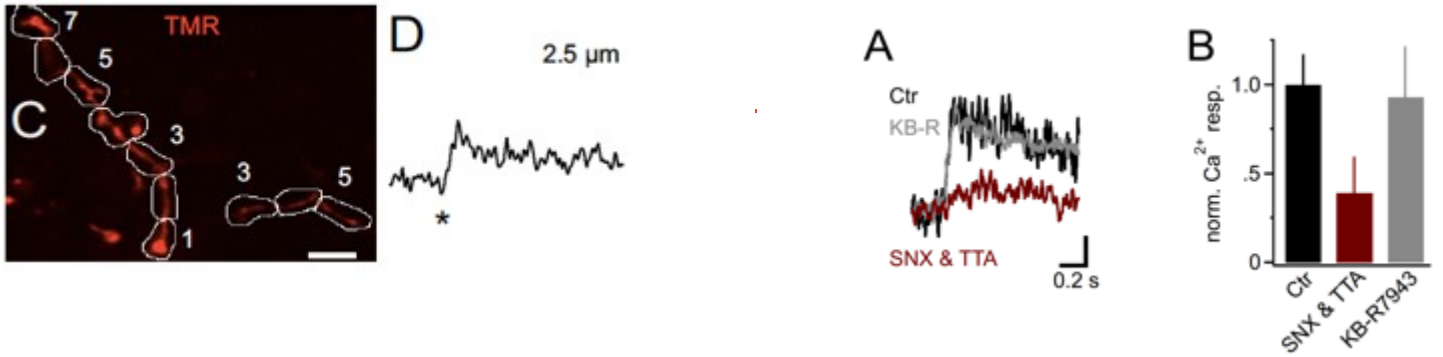
Wenjing Sun[1]*, Elizabeth A Matthews[1], Vicky Nicolas[1], Susanne Schoch[2], Dirk Dietrich[1]*

[1]Department of Neurosurgery, University Clinic Bonn, Bonn, Germany; [2]Department of Neuropathology, University Clinic Bonn, Bonn, Germany

Abstract Synaptic signaling to NG2-expressing oligodendrocyte precursor cells (NG2 cells) could be key to rendering myelination of axons dependent on neuronal activity, but it has remained unclear whether NG2 glial cells integrate and respond to synaptic input. Here we show that NG2 cells perform linear integration of glutamatergic synaptic inputs and respond with increasing dendritic calcium elevations. Synaptic activity induces rapid Ca^{2+} signals mediated by low-voltage activated Ca^{2+} channels under strict inhibitory control of voltage-gated A-type K^+ channels. Ca^{2+} signals can be global and originate throughout the cell. However, voltage-gated channels are also found in thin dendrites which act as compartmentalized processing units and generate local calcium transients. Taken together, the activity-dependent control of Ca^{2+} signals by A-type channels and the global versus local signaling domains make intracellular Ca^{2+} in NG2 cells a prime signaling molecule to transform neurotransmitter release into activity-dependent myelination.

DOI: 10.7554/eLife.16262.001

Ca^{2+} transients in dendrites are locally evoked and mediated through voltage-gated Ca^{2+} channels



Sun et al. *eLife* 2016

BJP British Journal of Pharmacology

Free Access

The plasma membrane Na^+/Ca^{2+} exchange inhibitor KB-R7943 is also a potent inhibitor of the mitochondrial Ca^{2+} uniporter

J Santo-Domingo, L Vay, E Hernández-SanMiguel, C D Lobatón, A Moreno, M Montero, J Alvarez

The Journal of Neuroscience
The Official Journal of the Society for Neuroscience

J Neurosci. 2014 Jul 9;34(28):9182–9189. doi: 10.1523/JNEUROSCI.0339-14.2014

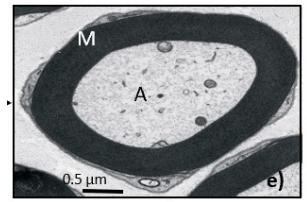
Inhibition of A-Type Potassium Current by the Peptide Toxin SNX-482

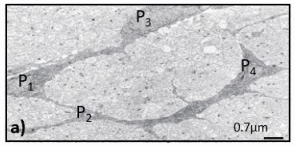
SUMMARY

OPCs exhibit Ca^{2+} excitability through local synaptic depolarization in dendrites and soma

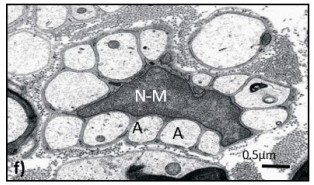
The activity-dependent control of Ca^{2+} signals by ion channels makes intracellular Ca^{2+} in OPCs a prime signaling molecule to transform neurotransmitter release into ***Activity-Dependent Myelination***

Schwann cells
development, maturation and differentiation





Castelnovo et al., Neural Regen Res 2017



Response of Schwann Cells to Action Potentials in Development

ATP/P2Y

Beth Stevens and R. Douglas Fields*

Sensory axons become functional late in development when Schwann cells (SC) stop proliferating and differentiate into distinct phenotypes. We report that impulse activity in premyelinated axons can inhibit proliferation and differentiation of SCs. This neuron-glial signaling is mediated by adenosine triphosphate acting through P2 receptors on SCs and intracellular signaling pathways involving Ca^{2+}, Ca^{2+}/calmodulin kinase, mitogen-activated protein kinase, cyclic adenosine 3′,5′-monophosphate response element binding protein, and expression of *c-fos* and *Krox-24*. Adenosine triphosphate arrests maturation of SCs in an immature morphological stage and prevents expression of O4, myelin basic protein, and the formation of myelin. Through this mechanism, functional activity in the developing nervous system could delay terminal differentiation of SCs until exposure to appropriate axon-derived signals.

www.sciencemag.org SCIENCE VOL 287 24 MARCH 2000

Rat Schwann Cells Express M1–M4 Muscarinic Receptor Subtypes

Ach/Musc

Simona Loreti,[1] M. Teresa Vilaró,[2] S. Visentin,[3] H. Rees,[4] Allan I. Levey,[4] and Ada Maria Tata[1]*

[1]Department of Cell and Developmental Biology, University "La Sapienza," Rome, Italy
[2]Department of Neurochemistry, Institut d'Investigacions Biomèdiques de Barcelona, CSIC, IDIBAPS, Barcelona, Spain
[3]Department of Cell Biology and Neuroscience, Istituto Superiore di Sanità, Rome, Italy
[4]Department of Neurology, Emory University School of Medicine, Atlanta, Georgia

The expression of different muscarinic receptor subtypes was analyzed in immature Schwann cells obtained from sciatic nerve of 2-day neonatal rats. By using RT-PCR analysis, we demonstrated the presence of M1, M2, M3, and M4 receptor subtypes in cultured Schwann cells, with M2 displaying the highest expression levels. Muscarinic subtypes were also quantified by immunoprecipitation and [^{3}H]QNB binding. With this approach, we found the levels of receptor expression to be M2 > M3 > M1. M4 is expressed at very low levels, and M5 receptor was not detectable. Moreover, we also demonstrated that stimulation of the receptors by muscarinic agonists activates previously described signal transduction pathways, leading to a decrease of cAMP and an increase of IP_3 levels not associated with an efficient intracellular Ca^{2+} release. The presence and activity of particular muscarinic receptors in immature Schwann cells suggest that ACh may play an important role in Schwann cell development.

Journal of Neuroscience Research 84:97–105 (2006)

Journal of Neuroscience Research

Purinergic Signaling Mediated by $P2X_7$ Receptors Controls Myelination in Sciatic Nerves

P2X7/P2X4

A. Faroni,[1,2]* R.J.P. Smith,[1,2] P. Procacci,[3] L.F. Castelnovo,[4] E. Puccianti,[3] A.J. Reid,[1] V. Magnaghi,[4] and A. Verkhratsky[2]

[1]Blond McIndoe Laboratories, Institute of Inflammation and Repair, University of Manchester, Manchester, United Kingdom
[2]Faculty of Life Sciences, University of Manchester, Manchester, United Kingdom
[3]Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Milan, Italy
[4]Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, Milan, Italy

Journal of Neuroscience Research 92:1259–1269 (2014)

Received: 22 March 2018 | Revised and accepted: 10 August 2018
DOI: 10.1002/glia.23527

GLIA
WILEY

RESEARCH ARTICLE

Overexpression of P2X4 receptor in Schwann cells promotes motor and sensory functional recovery and remyelination via BDNF secretion after nerve injury

Wen-Feng Su[1†] | Fan Wu[2†] | Zi-Han Jin[1†] | Yun Gu[1] | Ying-Ting Chen[1] | Ying Fei[1] | Hui Chen[1] | Ya-Xian Wang[1] | Ling-Yan Xing[1] | Ya-Yu Zhao[1] | Ying Yuan[1,3] | Xin Tang[1] | Gang Chen[1,4]

[1]Key Laboratory of Neuroregeneration of Jiangsu and Ministry of Education, Co-innovation Center of Neuroregeneration, Nantong University, Nantong, China
[2]Medical School of Nantong University, Nantong, China
[3]Affiliated Hospital of Nantong University, Nantong, China
[4]Department of Anesthesiology, Affiliated Hospital of Nantong University, Nantong, China

Correspondence
Gang Chen, Key Laboratory of Neuroregeneration of Jiangsu and Ministry of Education, Co-innovation Center of Neuroregeneration, Nantong University, Nantong 226001, China.
Email: chengang6626@ntu.edu.cn

Funding Information
The National Key Research and Development

Abstract
Of the seven P2X receptor subtypes, P2X4 receptor (P2X4R) is widely distributed in the central nervous system, including in neurons, astrocytes, and microglia. Accumulating evidence supports roles for P2X4R in the central nervous system, including regulating cell excitability, synaptic transmission, and neuropathic pain. However, little information is available about the distribution and function of P2X4R in the peripheral nervous system. In this study, we find that P2X4R is mainly localized in the lysosomes of Schwann cells in the peripheral nervous system. In cultured Schwann cells, TNF-α not only enhances the synthesis of P2X4R protein but also promotes P2X4R trafficking to the surface of Schwann cells. TNF-α-induced BDNF secretion in Schwann cells is P2X4R dependent. in vivo experiments reveal that expression of P2X4R in Schwann cells of injured nerves is strikingly upregulated following nerve crush injury. Moreover, overexpression of P2X4R in Schwann cells by genetic manipulation promotes motor and sensory functional recovery and accelerates nerve remyelination via BDNF release following nerve injury. Our results suggest that enhancement of P2X4R expression in Schwann cells after nerve injury may be an effective approach to facilitate the regrowth and remyelination of injured nerves.

Cellular/Molecular

Proteasomal Degradation of Glutamine Synthetase Regulates Schwann Cell Differentiation

GS/mGluR

Fuminori Saitoh and Toshiyuki Araki
Department of Peripheral Nervous System Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Tokyo 187-8502, Japan

Rapid saltatory nerve conduction is facilitated by myelin structure, which is composed of Schwann cells in the peripheral nervous system. Schwann cells drastically change their phenotype following peripheral nerve injury. These phenotypic changes are required for efficient degeneration/regeneration. We previously identified ZNRF1 as an E3 ubiquitin ligase containing a RING finger motif, whose expression is upregulated in the Schwann cells following nerve injury. This suggested that posttranscriptional regulation of protein expression in Schwann cells may be involved in their phenotypic changes during nerve degeneration/regeneration. Here we report the identification of glutamine synthetase (GS), an enzyme that synthesizes glutamine using glutamate and ammonia, as a substrate for E3 activity of ZNRF1 in Schwann cells. GS is known to be highly expressed in differentiated Schwann cells, but its functional significance has remained unclear. We found that during nerve degeneration/regeneration, GS expression is controlled mostly by ZNRF1-dependent proteasomal degradation. We also found that Schwann cells increase oxidative stress upon initiation of nerve degeneration, which promotes carbonylation and subsequent degradation of GS. Surprisingly, we discovered that GS expression regulates Schwann cell differentiation; i.e., increased GS expression promotes myelination via its enzymatic activity. Among the substrates and products of GS, increased glutamate concentration inhibited myelination and yet promoted Schwann cell proliferation by activating metabotropic glutamate receptor signaling. This would suggest that GS may exert its effect on Schwann cell differentiation by regulating glutamate concentration. These results indicate that the ZNRF1-GS system may play an important role in correlating Schwann cell metabolism with its differentiation.

SCIENTIFIC REPORTS

OPEN

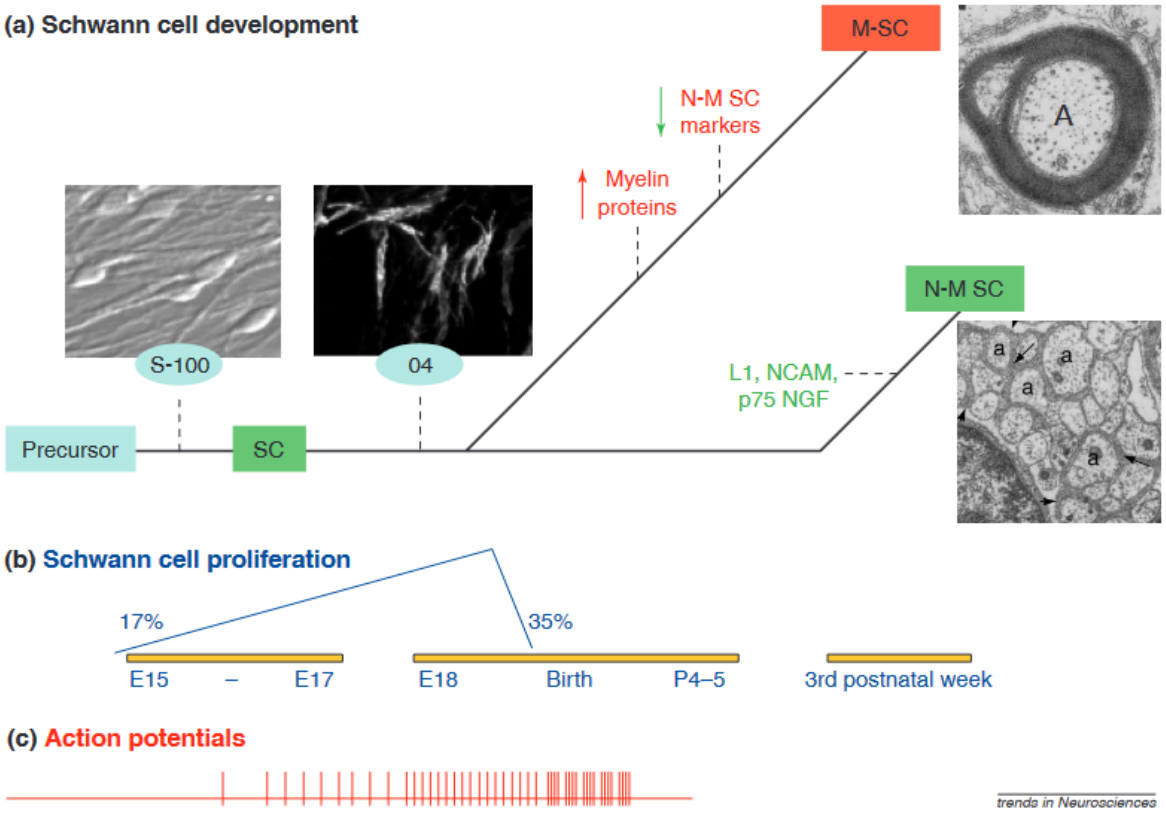
Glutamate signals through mGluR2 to control Schwann cell differentiation and proliferation

Received: 01 October 2015
Accepted: 27 June 2016
Published: 19 July 2016

Fuminori Saitoh[1,2], Shuji Wakatsuki[1], Shinji Tokunaga[1], Hiroki Fujieda[2] & Toshiyuki Araki[1]

Rapid saltatory nerve conduction is facilitated by myelin structure, which is produced by Schwann cells (SC) in the peripheral nervous system (PNS). Proper development and degeneration/regeneration after injury requires regulated phenotypic changes of SC. We have previously shown that glutamate can induce SC proliferation in culture. Here we show that glutamate signals through metabotropic glutamate receptor 2 (mGluR2) to induce Erk phosphorylation in SC. mGluR2-elicited Erk phosphorylation requires ErbB2/3 receptor tyrosine kinase phosphorylation to limit the signaling cascade that promotes phosphorylation of Erk, but not Akt. We found that Gβγ and Src are involved in subcellular signaling downstream of mGluR2. We also found that glutamate can transform myelinating SC to proliferating SC, while inhibition of mGluR2 signaling can inhibit demyelination of injured nerves *in vivo*. These data suggest pathophysiological significance of mGluR2 signaling in PNS and its possible therapeutic importance to combat demyelinating disorders including Charcot-Marie-Tooth disease.

SCIENTIFIC REPORTS | 6:29856 | DOI: 10.1038/srep29856



ATP: an extracellular signaling molecule between neurons and glia

R. Douglas Fields and Beth Stevens

Recent studies on Schwann cells at the neuromuscular junction and non-synaptic regions of premyelinated axons indicate that extracellular ATP can act as an activity-dependent signaling molecule in communication between neurons and glia. Several mechanisms have been observed for the regulated release of ATP from synaptic and non-synaptic regions, and a diverse family of receptors for extracellular ATP has been characterized. The findings suggest functional consequences of neuron–glial communication beyond homeostasis of the extracellular environment surrounding neurons, including regulating synaptic strength, gene expression, mitotic rate, and differentiation of glia according to impulse activity in neural circuits.

Trends Neurosci. (2000) 23, 625–633

Fig. 2. *Correlation between Schwann cell development and changes in neural impulse activity in dorsal root ganglion neurons of mouse during the perinatal period.* (a) Schwann cells precursors migrate out with the neural crest and begin to express the S-100 antigen. As they develop into immature Schwann cells they begin to express the 04 antigen, and then differentiate into either myelinating (M SC) or non-myelinating phenotypes (NM SC)[52]. (b) The rate of Schwann cell proliferation increases in late fetal development and begins to decrease near the time of birth[53]. (c) Action potentials from dorsal root ganglion (DRG) neurons show the onset of active spontaneous and sensory-evoked activity in DRG neurons coincides with the decrease in Schwann cells proliferation and differentiation[52]. ATP that is released by DRG neurons in culture inhibits Schwann cells proliferation and arrests development at a stage before development of the 04 antigen[3]. These correlations have yet to be tested in vivo, but suggest that impulse activity could stop proliferation and prevent terminal differentiation of Schwann cells until exposure to appropriate axon-specific differentiation signals. Adapted, with permission, from Ref. 51 and Ref. 68.

nature

Explore content | About the journal | Publish with us | Subscribe

nature > letters > article

Published: 01 September 1979

GABA may be a neurotransmitter in the vertebrate peripheral nervous system

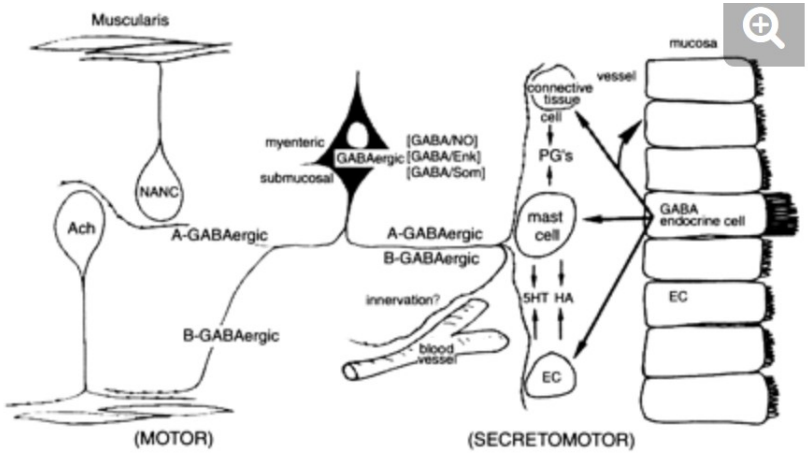
Kristján R. Jessen, Rhona Mirsky, Marion E. Dennison & Geoffrey Burnstock

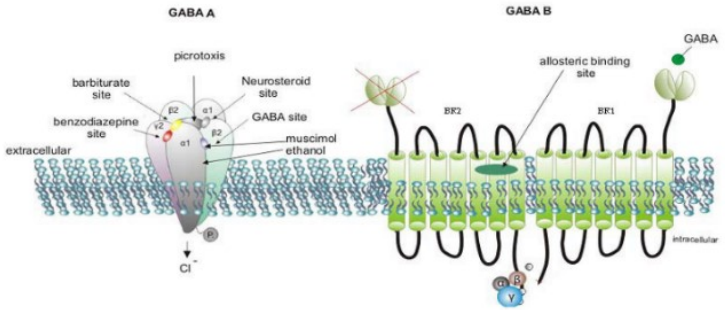
Nature **281**, 71–74 (1979) | Cite this article

374 Accesses | **221** Citations | Metrics

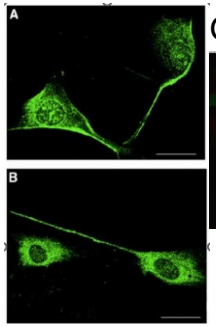
Abstract

γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter in the peripheral nervous system of certain invertebrates and is thought to be a major transmitter in the vertebrate central nervous system[1–3]. In this report we present evidence that GABA may also be a neurotransmitter in the vertebrate peripheral autonomie nervous system. We have used light and electron microscopic autoradiography to analyse high-affinity uptake of ^{3}H-GABA into the myenteric plexus of the guinea pig taenia coli, both *in situ* and in a tissue culture preparation. In the isolated myenteric plexus, we have measured the specific activity of glutamic acid decarboxylase (GAD; EC 4.1.1.15), the enzyme responsible for conversion of glutamic acid to GABA in GABAergic neurones[4,5], and assessed the ability of this tissue to accumulate ^{3}H-GABA newly synthesised from ^{3}H-glutamic acid. Furthermore, we have measured the levels of endogenous GABA in strips of taenia coli containing the myenteric plexus.



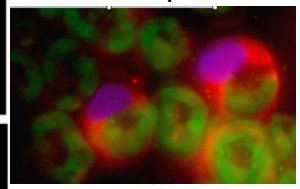


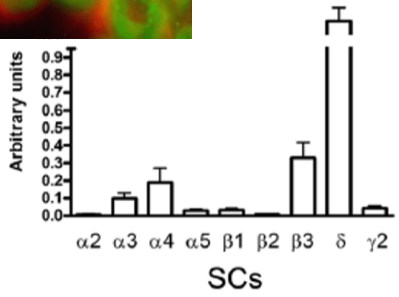
Melcangi RC et al, JNR 1999
Magnaghi V. et al, E.J.N. 2004
Magnaghi V. et al, Brain Res. Rev. 2005
Magnaghi et al., JMN 2006
Magnaghi et al. Mol Cell Neurosci 2008
Magnaghi V. et al., J Neurochem. 2010
Perego C. et al. J. Cell Physiol 2011
Faroni A. J Mol Neurosci. 2012
Magnaghi V. et al. Front Cell Neurosci 2013
Faroni A. et al. GLIA 2014
Melfi S. et al. Molec. Neurobiol. 2018
Faroni A et al Mol Neurobiol 2019

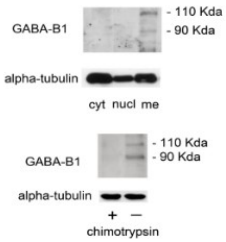


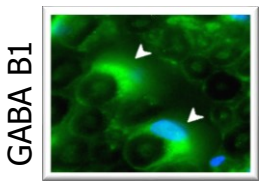
GABA A-alpha3

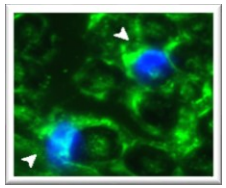
GABA A-alpha2

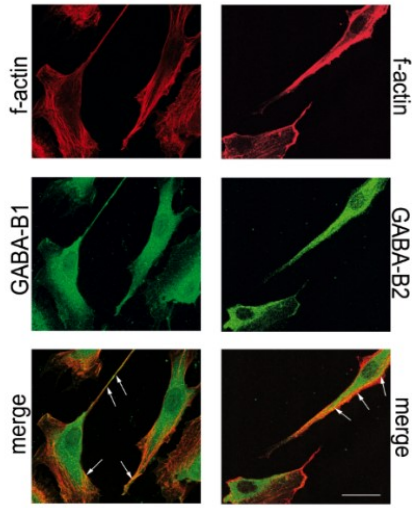




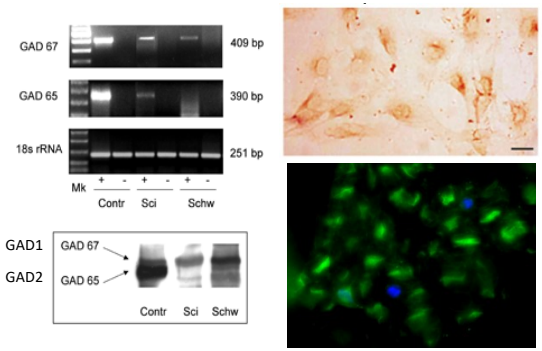


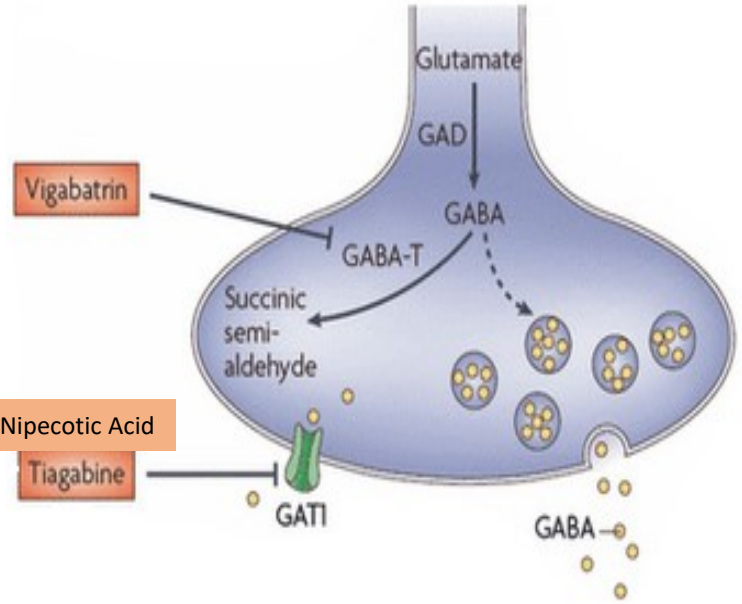






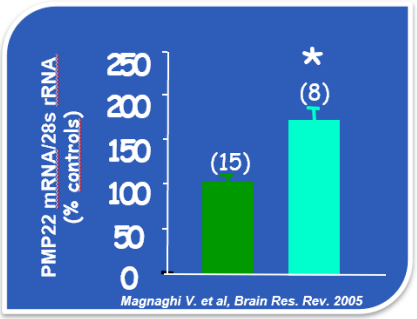
GAD65/GAD67



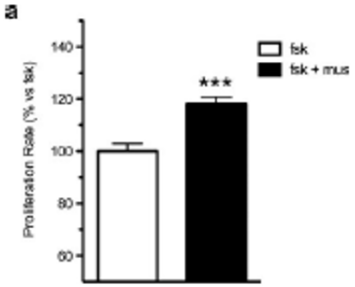


GABA

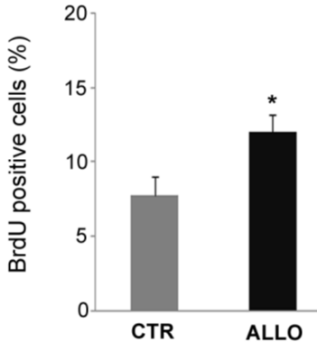
released from SCs



PMP22 GENE EXPRESSION IN SCHWANN CELL 24 h AFTER EXPOSURE TO GABA-A RECEPTOR AGONIST **MUSCIMOL**

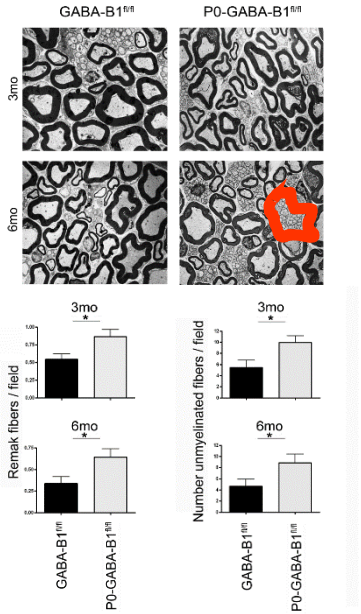


SCHWANN CELL PROLIFERATION AFTER EXPOSURE TO GABA-A RECEPTOR AGONIST **MUSCIMOL**



GABA-A rec (medium/long-term) increases the proliferation and the myelin proteins expression in Schw cells

conditional KO GABA-B1



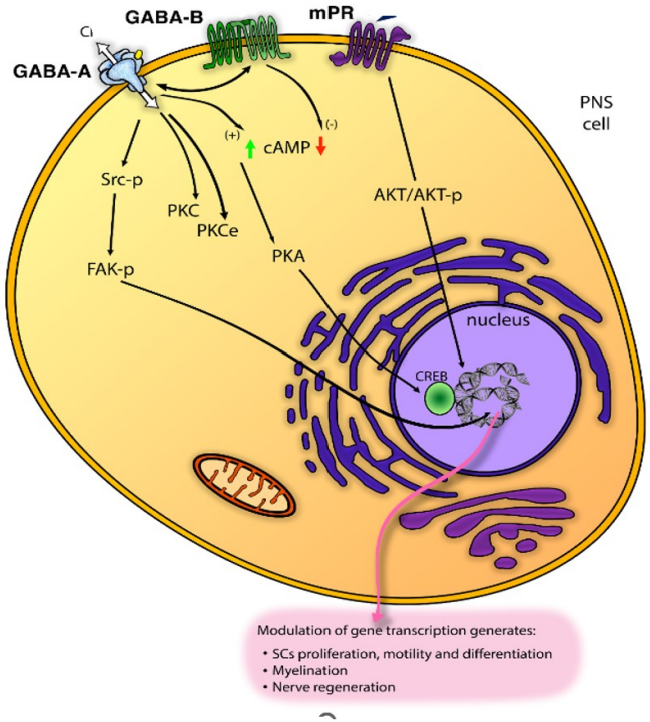
*…..shift **myelinated Abeta/delta** vs **C fibers***

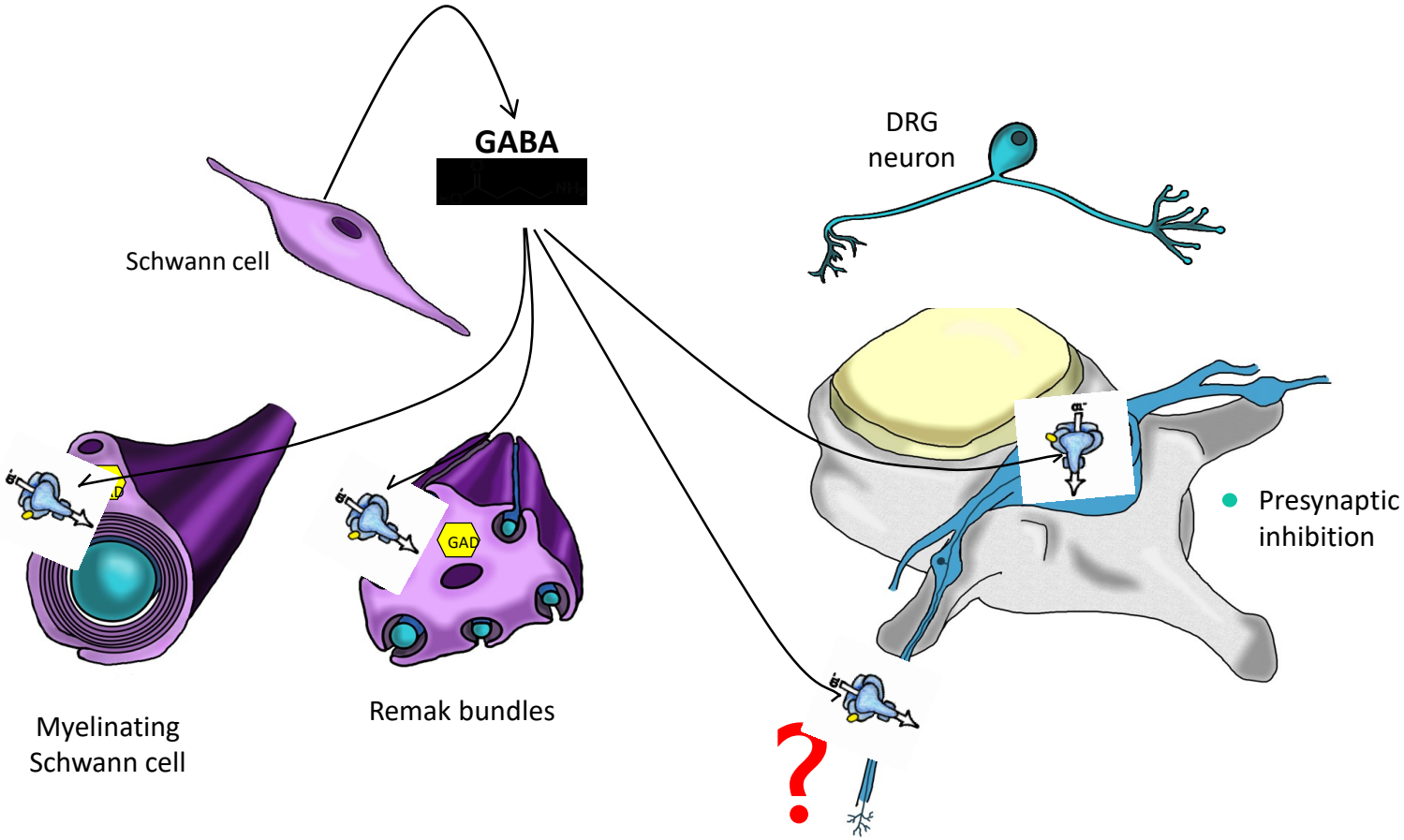
GABA machinery is present in the Schwann cells of the PNS

The Schwann cells are a target but also a source of GABA (synthesis, uptake and release)

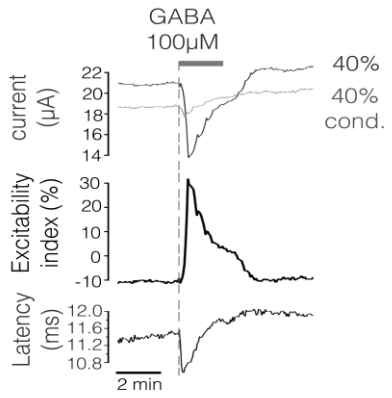
GABA-A rec, via PK-A and PK-C signalling, controls the GABA synthesis and supplies an autocrine loop that in turn regulates proliferation and myelination

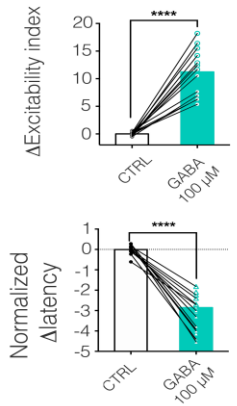
GABA-B rec, NRG1-3/Erb signaling, controls the number of unmyelinated fibers likely participating in axonal sorting and nociception

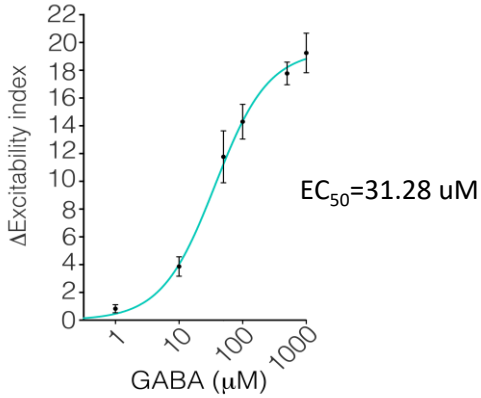


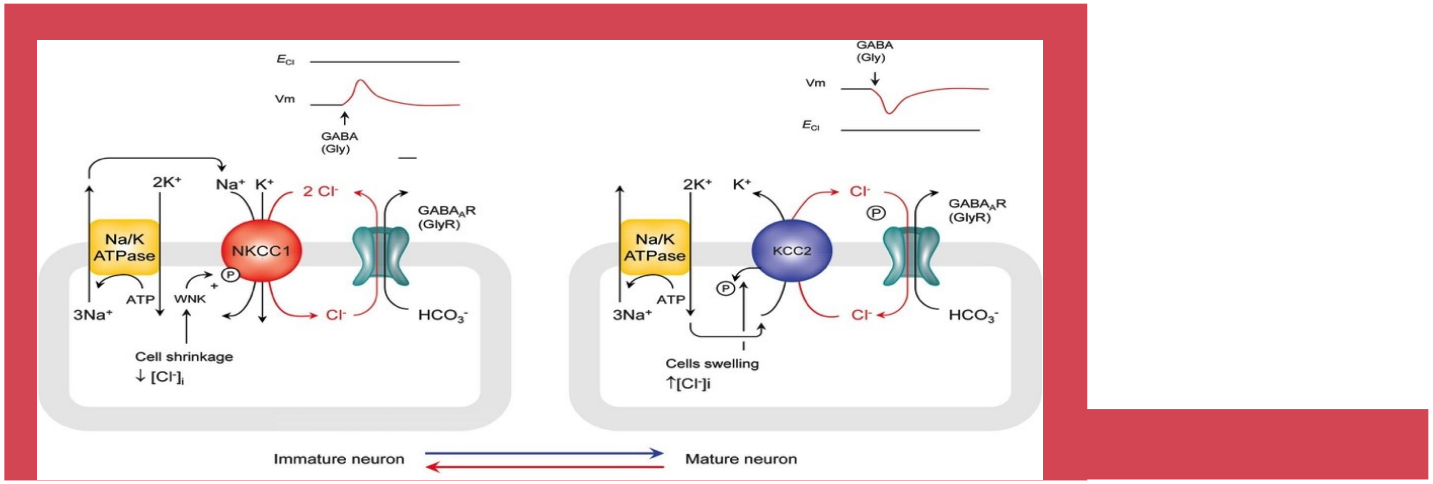

GABA
Schwann cell
DRG
neuron
GAD
Presynaptic
inhibition
Myelinating
Schwann cell
Remak bundles
?

GABA generates an axonal depolarization in peripheral sensory C fibers



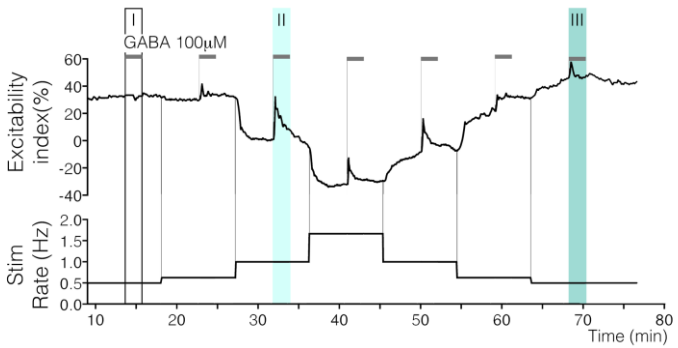


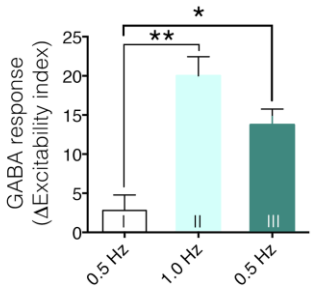




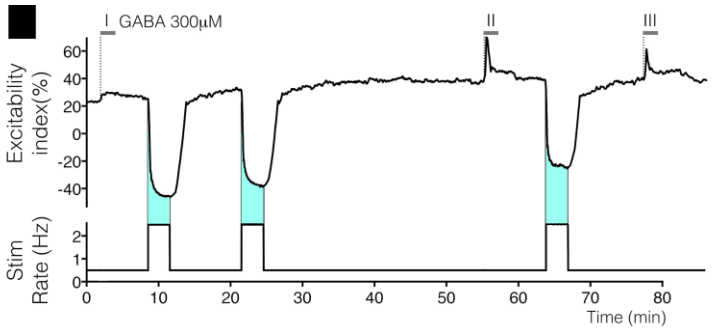
Bonalume et al. J Physiol 2021

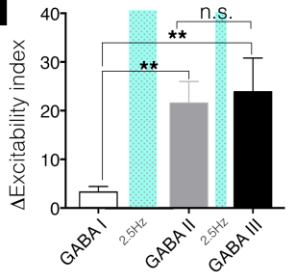
GABA depolarization is activity dependent and long-lasting





The high-freq stimulation (up to 2.5 Hz) potentiates the GABA-evoked currents



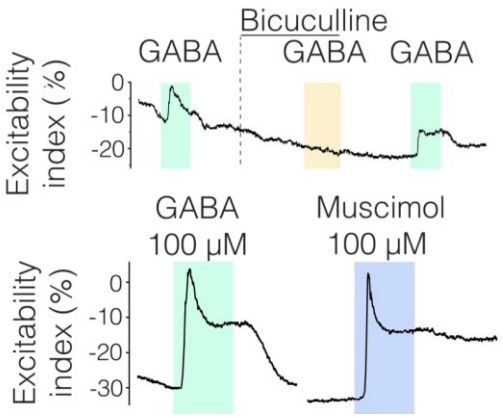


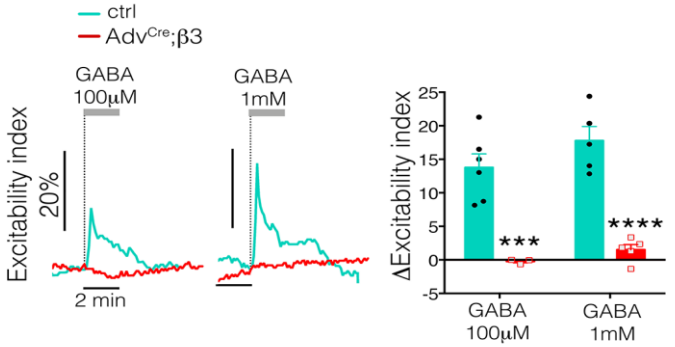
This activity dependent sensitization to GABA is long-lasting

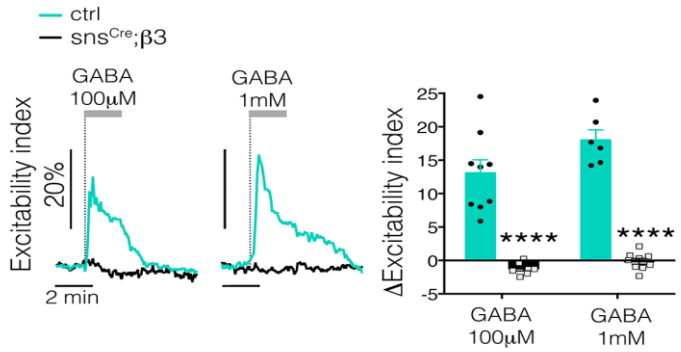
…..GABA-evoked TONIC depolarization along C-fibers!!

Bonalume et al. J Physiol 2021

GABA generates a depolarization in peripheral sensory C fibers

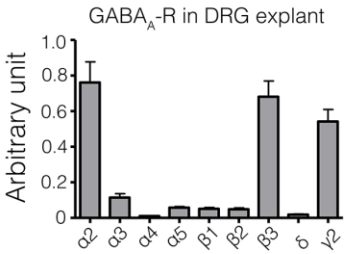




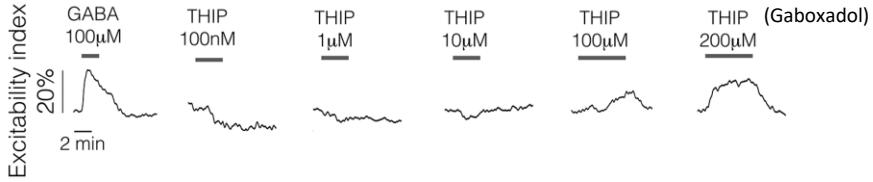


Bonalume et al. J Physiol 2021

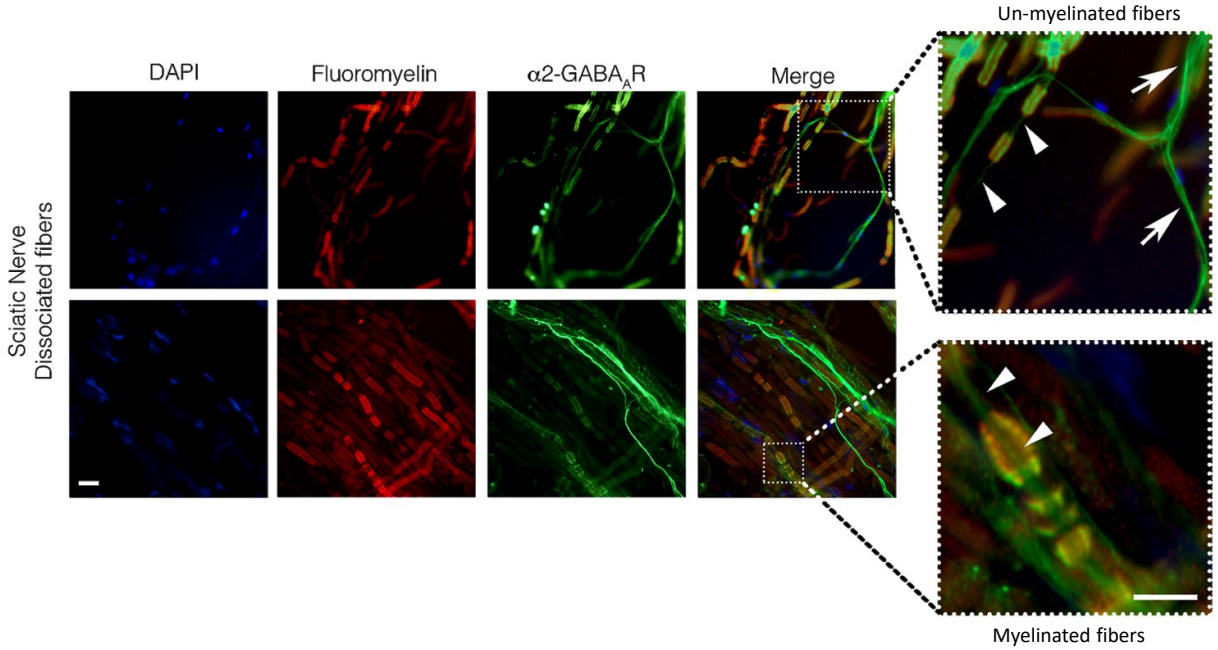
Axonal $GABA_AR$ composition in PNS



subunit expression



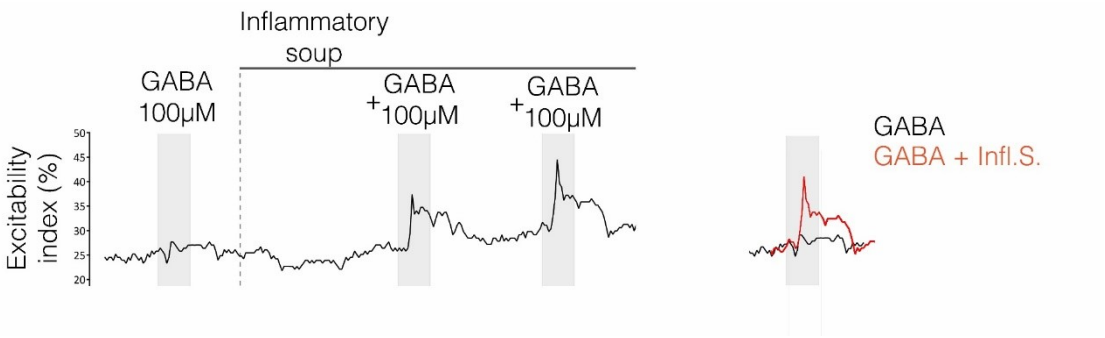
specific pharmacology: gaboxadol… δ-subunit



the peripheral axonal $GABA_AR$ in nociceptor is mainly formed by a **α2β3γ2** constellation

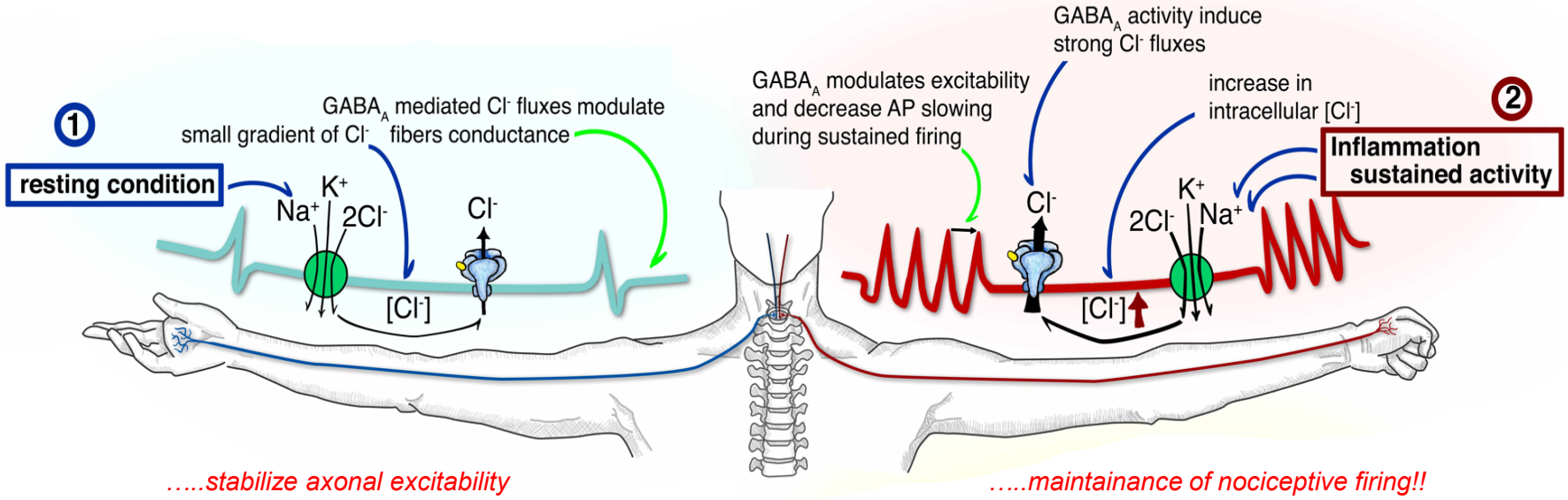
GABA-evoked depolarization is potentiated by inflammation:

evident and fast depolarization …



INFLAMMATION: acute and chronic pain

Bonalume et al. J Physiol 2021



Bonalume and Magnaghi, Neural Reg Res 2023

SUMMARY of GABA cross-talk in PNS

- GABA is synthesized and released by Schwann cells
- GABA depolarizes nerve axons and enhances C-fiber excitability via GABA-A rec
- Action potential activity in unmyelinated C-fiber is coupled to NKCC1 activity and Cl- flux
- NKCC1 maintains feedforward stabilisation of C-fiber excitability and allows sustained firing, even during inflammation