Abstract #699

Peripheral nervous system glia modulates excitability of nociceptive axons *via* $GABA_A$ receptor

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Content

Schwan cells (SCs) synthesize GABA and express GABA receptors, possessing functional roles in cell differentiation, proliferation and myelination. GABA classically inhibits synaptic transmission in the central nervous system while its function in peripheral axons is unclear.

Therefore, we performed an electrophysiological characterization of $GABA_A$ receptors in peripheral axons, concentrating on unmyelinated C-fibers. $GABA_A$ receptor activation resulted in axonal depolarization. Using conditional NaV1.8 $GABA_A$-β3 null mice we demonstrated that this effect was mediated by $GABA_A$ receptors and restricted to nociceptors.

We functionally identified axonal $GABA_A$ as a novel player in neuron-glia cross talk by demonstrating that axonal $GABA_A$ can be modulated directly and indirectly by endogenous agonists, such as GABA and the neuroactive steroid allopregnanolone (ALLO) synthesized by Schwann cells. We showed that endogenous GABA can mitigate the loss of axonal excitability observed in C-fibre nociceptors during sustained firing. Furthermore, ALLO exerts dual actions on C-fibers excitability. On the one hand, ALLO allosterically modulates axonal $GABA_A$ receptors increasing the efficacy of GABA agonists. Over a longer time course, ALLO activates a paracrine mechanism able to desensitize $GABA_A$ at a later stage. Indeed, ALLO causes the enhancement of BDNF production by SCs and the subsequent trk-B mediated up-regulation of PKCε in DRG neurons, leading to $GABA_A$ phosphorylation and desensitization.

Overall, we suggest that SCs are actively involved in the local regulation of peripheral nociceptive signaling along peripheral axons targeting axonal $GABA_A$ receptors through the synthesis of GABA, ALLO and BDNF.

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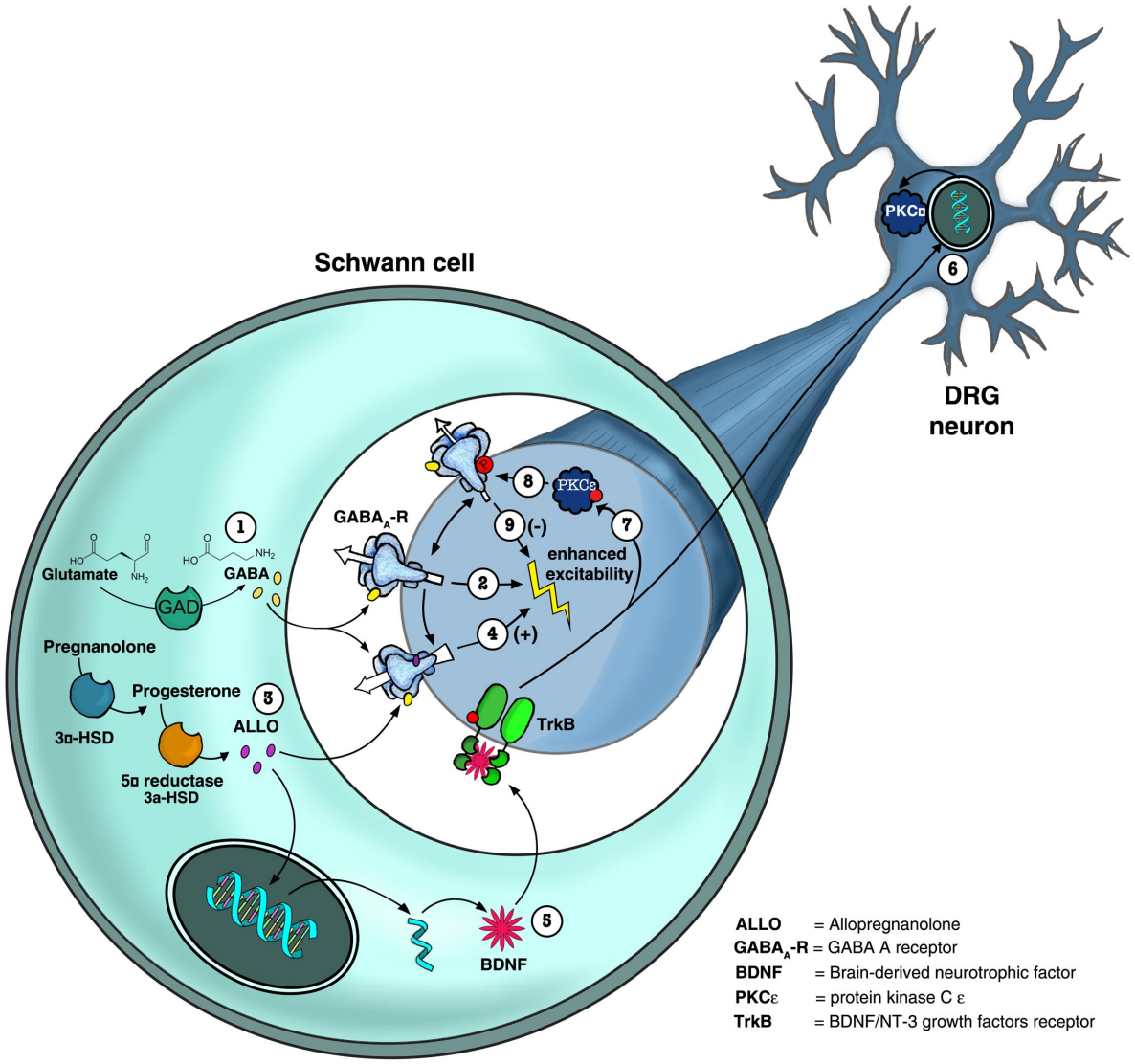
Schwann cell
DRG neuron
PKCα
6
GABA$_A$-R
8
PKCε
9
(-)
7
enhanced excitability
2
4
(+)
TrkB
1
Glutamate
GABA
GAD
Pregnanolone
Progesterone
3
ALLO
3α-HSD
5α reductase
3a-HSD
5
BDNF
ALLO = Allopregnanolone
GABA$_A$-R = GABA A receptor
BDNF = Brain-derived neurotrophic factor
PKCε = protein kinase C ε
TrkB = BDNF/NT-3 growth factors receptor