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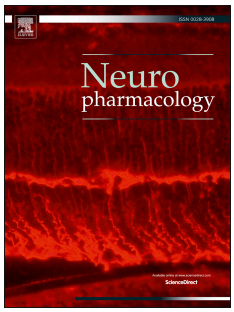

In vitro gamma oscillations following partial and complete ablation of δ subunit-containing $GABA_A$ receptors from parvalbumin interneurons

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Abstract

Perisynaptic and extrasynaptic δ subunit-containing $GABA_A$ receptors (δ-$GABA_A$Rs) mediate tonic conductances in many neurons. On principal cells of the neocortex and hippocampus they comprise α4 subunits, whereas they usually contain α1 on various interneurons. Specific characteristics of δ-$GABA_A$Rs are their pharmacology and high plasticity. In particular δ-$GABA_A$Rs are sensitive to low concentrations of neurosteroids (NS) and during times of altered NS production (stress, puberty, ovarian cycle and pregnancy) δ-$GABA_A$Rs expression varies in many neurons regardless of the α subunits they contain, with direct consequences for neuronal excitability and network synchrony. For example δ-$GABA_A$Rs plasticity on INs underlies modifications in hippocampal γ oscillations during pregnancy or over the ovarian cycle.

Most δ-$GABA_A$R-expressing INs in CA3 stratum pyramidale (SP) are parvalbumin (PV)+INs, whose fundamental role in γ oscillations generation and control has been extensively investigated. In this study we reduced or deleted δ-subunits in PV+INs, with the use of a PV/*Cre-Gabrd*/floxed genetic system. We find that *in vitro* CA3 γ oscillations of both PV-*Gabrd*$^{+/-}$ and PV-*Gabrd*$^{-/-}$ mice are characterized by higher frequencies than WT controls. The increased frequencies could be lowered to control levels in PV-*Gabrd*$^{+/-}$ by the NS allopregnanolone (3α,5α-tetrahydroprogesterone, 100 nM) but not the synthetic δ-$GABA_A$R positive allosteric modulator 4-Chloro-N-[2-(2-thienyl)imidazo[1,2-a]pyridin-3-yl] benzamide (DS-2, 10 μM). This is consistent with the idea that DS-2, in contrast to ALLO, selectively targets α4/δ-$GABA_A$Rs but not the α1/δ-$GABA_A$Rs found on INs. Therefore, development of drugs selective for IN-specific α1/δ-$GABA_A$Rs may be useful in neurological and psychiatric conditions correlated with altered PV+IN function and aberrant γ oscillations.

Highlights

1) In the CA3 network γ frequency modulation is possible through NS potentiation of δ-$GABA_A$Rs on PV+INs.
2) Increase in *in vitro* CA3 γ oscillation frequencies in both PV-*Gabrd*$^{+/-}$ and PV-*Gabrd*$^{-/-}$.
3) Endogenous NS ALLO decreases γ oscillation frequencies in PV-*Gabrd*$^{+/-}$ mice.
4) DS-2 does not potentiate the α1/δ-$GABA_A$Rs of PV+INs.
5) Opens the possibility for the development of α1/δ-$GABA_A$Rs-specifc drugs for disorders comprising IN dysfunction.