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MEETING ABSTRACT

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The presynaptic calcium channel subunit $\alpha_2\delta$-2 regulates postsynaptic $GABA_A$-receptor abundance and axonal wiring by a trans-synaptic mechanism

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Background: Auxiliary $\alpha_2\delta$ subunits modulate membrane expression and current properties of voltage-gated calcium channels (VGCCs) and have been implicated in synapse formation. Indeed, by employing a cellular $\alpha_2\delta$ triple knockout model in cultured hippocampal neurons, we could identify $\alpha_2\delta$ isoforms as redundant key regulators of glutamatergic synaptogenesis (Schöpf *et al.*, submitted). However, their role in inhibitory synapses remained so far elusive.
Hypothesis: Here we show that the specific expression of a single isoform, $\alpha_2\delta$-2, in presynaptic glutamatergic terminals induces a mismatched localization of postsynaptic $GABA_A$ receptors ($GABA_A$Rs). In theory, this puzzling observation may be explained by (1) a compensatory upregulation of postsynaptic $GABA_A$Rs, (2) an active participation of presynaptic $\alpha_2\delta$-2 in the transsynaptic anchoring of postsynaptic $GABA_A$Rs, and (3) aberrant axonal wiring induced by presynaptic expression of $\alpha_2\delta$-2.
Methods: In order to distinguish between these hypotheses, primary mouse neuronal cultures were transfected with individual $\alpha_2\delta$ isoforms together with soluble eGFP. Using immunofluorescence and patch-clamp analysis the consequences of presynaptic $\alpha_2\delta$ expression on glutamatergic and GABAergic synapse composition and synaptic transmission were studied.
Results: We show that presynaptic $\alpha_2\delta$-2 increases postsynaptic $GABA_A$Rs both in glutamatergic and GABAergic synapses. This effect is even stronger in hippocampal cultures lacking the prototypical cell-adhesion molecules α-neurexins, which are tightly associated with neuronal VGCC functions. Therefore, while α-neurexins modulate the effect of presynaptic $\alpha_2\delta$-2, they are not needed for recruiting $GABA_A$Rs by $\alpha_2\delta$-2. Importantly, employing high- and super-resolution (gSTED) microscopy we demonstrate that presynaptic expression of $\alpha_2\delta$-2 induces aberrant wiring of glutamatergic axons to GABAergic postsynaptic positions, resulting in altered synaptic transmission. Finally, using structure homology modeling and immunofluorescence analysis we identify a single splice region in $\alpha_2\delta$-2 responsible for mediating the transsynaptic effect on $GABA_A$Rs.
Conclusion: Our results point towards an active involvement of $\alpha_2\delta$-2 in axonal wiring and the recruitment and/or anchoring of postsynaptic $GABA_A$Rs. Thus, the findings presented here provide novel insights into transsynaptic mechanisms and may explain how abnormal $\alpha_2\delta$ subunit expression can result in aberrant neuronal wiring associated with neurological disorders, including epilepsy and autism.
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