## Gephyrin-interacting molecules

<table>
<thead>
<tr>
<th>Full name</th>
<th>Description</th>
<th>Role of interaction</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td>Calpain</td>
<td>Ca**+**- and ERK-dependent serine proteases enriched in the CNS and with a broad substrate specificity</td>
<td>Cleaves gephyrin in a manner regulated by phosphorylation of Ser268 and Ser270</td>
<td>1</td>
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<tr>
<td>Cyclin-dependent kinase 5 (CDK5)</td>
<td>Ser/Thr kinase</td>
<td>Phosphorylates gephyrin residue Ser270 in a collybistin-dependent manner</td>
<td>2</td>
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<tr>
<td>Collybistin*</td>
<td>Guanine exchange factor; member of the Dbl family</td>
<td>Essential for gephyrin clustering in most GABAergic synapses; selectively activates CDC42</td>
<td>3-7</td>
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<tr>
<td>Cell division control protein 42 homolog (CDC42)</td>
<td>Small GTPase of the Rho family</td>
<td>Modulates gephyrin postsynaptic cluster size and shape, in conjunction with CB</td>
<td>8,9</td>
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<tr>
<td>Dynein light chain 1&amp;2 – Protein inhibitor of neuronal nitric oxide synthase (PIN)*</td>
<td>Accessory proteins of the dynein motor complex; protein inhibitor of nNOS</td>
<td>Their role in gephyrin transport is not clear; PIN might regulate nNOS activity at GABAergic synapses</td>
<td>10,11</td>
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<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt; receptor α1, α2, α3, β2, β3 subunits*</td>
<td>Subunits contributing to GABA&lt;sub&gt;A&lt;/sub&gt;R subtypes mediating phasic inhibition</td>
<td>Involved in region specific localization of specific GABA&lt;sub&gt;A&lt;/sub&gt;R subunits in neurons and initiating gephyrin clustering at synapses</td>
<td>13-18</td>
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<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt; Receptor Associated Protein (GABARAP)*</td>
<td>Member of the autophagy-related protein 8 family; sequence homology with MAP1 LC3</td>
<td>Initially it was thought to link gephyrin with GABA&lt;sub&gt;A&lt;/sub&gt;R subunit (γ2); however, it facilitates cell surface expression of GABA&lt;sub&gt;A&lt;/sub&gt;R and regulates anterograde transport along with KIF5</td>
<td>19-21</td>
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<tr>
<td>Glycine receptor β subunit*</td>
<td>GlyR subunit contributing to heteromeric receptors</td>
<td>High affinity binding site, required for postsynaptic clustering of heteromeric GlyR</td>
<td>22,23</td>
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<tr>
<td>Glutamate Receptor Interacting Proteins (GRIP)</td>
<td>PDZ-domain containing proteins located in glutamatergic and GABAergic PSDs, interacting with numerous proteins involved in trafficking and localization of synaptic proteins</td>
<td>Function of GRIP at GABAergic synapses is presently unclear.</td>
<td>24,25</td>
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<tr>
<td>Glycogen Synthase Kinase 3β (GSK3β)</td>
<td>Proline-directed Ser/Thr kinase involved in energy metabolism, neuronal cell development, and body pattern formation</td>
<td>Targets Ser270 of gephyrin to regulate formation of postsynaptic clusters and density of GABAergic synapses</td>
<td>1,12</td>
</tr>
<tr>
<td>Heat Shock Cognate 71kDa Protein (HSC70)</td>
<td>Chaperone; repressor of transcriptional activation</td>
<td>Direct interaction with gephyrin (G-domain); overexpression interferes with gephyrin, but not GlyR clustering</td>
<td>26</td>
</tr>
<tr>
<td>Integrins β1 and β3</td>
<td>Membrane proteins connecting extracellular matrix (ECM) to intracellular signaling. They play an important role in LTP and spatial memory.</td>
<td>β1 and β3 integrins signal in opposite directions to regulate gephyrin and GlyR clustering in spinal cord neurons in a GαMKII, thrombospondin 1 and fibrinogen dependent mechanism.</td>
<td>27,28</td>
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</table>
### KIF5
Accessory protein of kinesin-based motor complexes
Contributes to anterograde transport of gephyrin/GlyR complexes, as well as GABA<sub>A</sub>R/HAP1 and GABA<sub>A</sub>R/GABARAP/gephyrin complexes
20,29,30

### Mena/Vasp*
Proteins regulating actin polymerization
Postulated to contribute to gephyrin binding to microfilaments
31,32

### Mammalian Target of Rapamycin (mTOR)
Serine/threonine protein kinase regulating cell growth, proliferation, survival, motility, protein synthesis, and transcription
Unknown; gephyrin postulated to regulate mTOR activity
33,34

### Neurilglin2 (NLGN2)*
Member of the neurilgin family, preferentially located at GABAergic synapses
NL2 binding to gephyrin might trigger formation of postsynaptic clusters; it contributes to post-synaptic aggregation of α1-GABA<sub>A</sub>R in absence of gephyrin
35-37

### Peptidyl-prolyl cis/trans isomerase 1 (Pin1)*
Isomerizes serine and threonine residues post-phosphorylation
Postulated to regulate gephyrin conformation and interaction with GlyR in a phosphorylation-dependent manner
38

### Protein phosphatase 1
Serine/threonine phosphatase with a 30kDa catalytic subunit that can interact with diverse regulatory subunits
Regulates gephyrin clustering; targeted residues not identified.
39

### Profilin
Regulates actin dynamics and turnover; binds proline-rich domains, and phosphoinositides in the plasma membrane
Postulated to contribute to anchoring gephyrin to actin microfilaments
32,40

### Vacuolar sorting protein 35 /Neurobeachin
Contribute to protein sorting and transport, and to synapse delivery of neurotransmitter receptors
Postulated to contribute to gephyrin and GlyR trafficking to the synapse
41

### WAVE-associated Rac GTPase Activating Protein (WRP)/SLIT-ROBO Rho GTPase-activating protein 2 (srGAP2)
Homologous small GTPases of the Rho family
Identified in a screen of SH3 domain interacting proteins; facilitates gephyrin and GABA<sub>A</sub>R postsynaptic clustering
42

* indicates that the localization of the binding site on gephyrin is known

### References

7. Harvey, K. et al. The GDP-GTP exchange factor collybistin: an essential determinant of neuronal

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Supplementary Information


