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Metabotropic glutamate receptor 4 interacts with microtubule-associated protein 1B

Anina Moritz [a,1], Astrid Scheschonka [a], Tobias Beckhaus [b], Michael Karas [b], Heinrich Betz [a,*]

[a] Department of Neurochemistry, Max-Planck-Institute for Brain Research, Deutschordenstrasse 46, 60528 Frankfurt, Germany
[b] Institute of Pharmaceutical Chemistry, Johann Wolfgang Goethe University, D-60438 Frankfurt am Main, Germany

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ABSTRACT

The metabotropic glutamate receptor 4 (mGluR4) is a G-protein-coupled receptor that mediates inhibition of neurotransmitter release. Here, we used a proteomic approach to identify novel interaction partners of mGluR4 and report that the cytoplasmic C-terminal tail of mGluR4 interacts with microtubule-associated protein 1B (MAP1B). Binding of MAP1B to mGluR4 is inhibited by Ca^{2+}/calmodulin, and MAP1B and mGluR4 colocalize at excitatory synapses in cultured hippocampal neurons. Thus, MAP1B might be implicated in the synaptic trafficking and/or regulation of mGluR4.

Introduction

Metabotropic glutamate receptors (mGluRs) constitute a family of eight G-protein-coupled receptors (GPCRs) that are involved in the modulation of synaptic transmission [1]. mGluRs of the predominantly presynaptically localized sub-group III comprising mGluR4, mGluR6, mGluR7 and mGluR8 inhibit adenylylcyclase via $G\alpha_i$ and are selectively activated by L-AP4. Their major function is the feedback regulation of glutamate release.

Different studies have shown that the intracellular C-termini of mGluRs are important binding sites for interacting proteins (reviewed in [2]). The latter may regulate processes as diverse as down-stream signal transduction, receptor trafficking and anchoring to the cytoskeleton. For example, Ca^{2+}/calmodulin (CaM) has been shown to compete with G-protein $\beta\gamma$-subunit binding to mGluR7 and other group III mGluRs [3] and is thought to facilitate mGluR-mediated inhibition of presynaptic Ca^{2+} channels upon activity-induced Ca^{2+} influx [4,5]. Yeast two-hybrid screens have revealed interactions of mGluR8 with PIAS1 [6], and of mGluR7 with the protein interacting with C-kinase 1 (PICK1) [2]. The latter interaction has been found to be important for receptor stability [7], down-stream signalling [8] and anti-epileptogenic activity [9].

mGluR4 belongs to the least characterized group III mGluRs although it constitutes a potential target for novel therapeutics, in particular in Parkinson's disease [10]. mGluR4 activation provides neuroprotection in models of excitotoxicity [11] and dopaminergic neuron degeneration [12]. Mice deficient in mGluR4 show resistance to GABA-A receptor antagonist induced absence seizures [13], and increased mGluR4 levels have been found in human temporal lobe epilepsy [14]. Here, we describe a proteomic approach for identifying mGluR4 binding proteins and show that microtubule-associated protein 1B (MAP1B) is a novel interaction partner of mGluR4.

Materials and methods

Animals and antibodies. Adult Wistar rats and wild-type (C57/BL6) and mGluR4 −/− mice [15] backcrossed to the C57/BL6 background were deeply anaesthesized and killed by decapitation in accordance with national regulations. Brains were dissected, frozen in liquid nitrogen and stored at −80 °C. Primary antibodies used were a rabbit polyclonal antibody raised against amino acids 893–912 of rat mGluR4 (Upstate), a mouse monoclonal antibody AA6 against MAP1B (Sigma), and a guinea pig polyclonal antibody against the vesicular glutamate transporter 1 (vGluT1; Chemicon). Secondary antibodies were Alexa goat anti-rabbit-488, anti-guinea-pig-546, anti-mouse-488, and anti-rabbit-546 (all from Molecular Probes).

GST pull-down assays. The glutathione-*S*-transferase (GST) fusion protein expression constructs and the protocols for protein expression and purification have been described previously [3,6,16]. Rat brains were homogenized in ice-cold TBS (50 mM Tris buffer, pH 7.4, 125 mM NaCl) containing 100 μM phenylmethylsulfonyl fluoride and complete protease inhibitor cocktail (Roche). After centrifugation at 3500*g* for 10 min at 4 °C, the supernatant (S1) was adjusted to 1% (v/v) Triton X-100 and re-centrifuged at 15,000*g* for 30 min to result in supernatant S2.

* Corresponding author. Fax: +49 69 96769 441.
E-mail address: neurochemie@mpih-frankfurt.mpg.de (H. Betz).
[1] Present address: Laboratoire de Neurobiologie, CNRS UMR 7637, École Supérieure de Physique et de Chimie Industrielles, 10 Rue Vauquelin, 75005 Paris, France.

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Glutathione-Sepharose beads (GE Healthcare Europe) were incubated with GST fusion protein for 1 h at 4 °C, washed, and re-incubated overnight with S2 fractions at 4 °C. Where indicated, calmodulin and Ca^{2+} or EGTA were added to the S2 fraction before adding the immobilized GST fusion protein. After washing with TBS, bound proteins were eluted with SDS-sample buffer and analyzed by SDS–PAGE followed by silver staining or Western blotting. Loading of equal amounts of GST fusion proteins was confirmed by Ponceau S staining of the blot membranes.

Protein identification by mass spectrometry. Silver-stained protein bands were excised from SDS–polyacrylamide gels, processed for mass spectrometry (MS) and identified by MALDI-TOF-MS and tandem MALDI-TOF/TOF-MS as described [17].

Co-immunoprecipitation. Freshly dissected C57/BL6 mouse brains were homogenized in TBS containing 100 μM phenylmethylsulfonyl fluoride and complete protease inhibitor cocktail (Roche) followed by centrifugation at 2000*g* for 10 min. The supernatant was re-centrifuged at 100,000*g* for 1 h and the resulting pellet solubilized for 4 h in 1% (v/v) Triton X-100 in TBS. After centrifugation for 30 min at 14,000*g*, the resulting detergent extract was precleared by incubation with protein G-Sepharose (GE Healthcare, Europe). After incubation with antibodies against MAP1B (1:1000) for 2 h, antigen–antibody complexes were immobilized on protein G-Sepharose overnight. All steps were performed at 4 °C. After washing the beads with 0.05% (v/v) Tween 20 in 50 mM Tris/HCl, pH 7.4, 150 mM NaCl (TBS-T), bound proteins were eluted with 2× SDS-sample buffer and analyzed by Western blotting with mGluR4 antibody.

SDS–PAGE and Western blotting. Protein samples were separated on 6–8% SDS–polyacrylamide gels (PROTEAN II xi or Mini-PROTEAN III system, Bio-Rad) and silver-stained using the Silver Stain Plus Kit (Bio-Rad). Western blotting with anti-MAP1B (1:500) and anti-mGluR4 (1:1000) was performed as described [3].

Primary cultures and immunofluorescence staining of rat hippocampal neurons. Hippocampal neurons were cultured as previously described [18]. Neurons were fixed with 100% methanol at −20 °C. Cells were permeabilized with 0.2% (v/v) Triton X-100 for 20 min and then blocked with 5% (w/v) goat serum in TBS for 1 h. Incubation with primary antibodies was at 4 °C in blocking buffer for at least 24 h, and with secondary antibodies for 45 min, respectively. Antibody dilutions were 1:200 (anti-MAP1B), 1:100 (anti-mGluR4), 1:200 (anti-vGluT1), and 1:1000 (secondary antibodies). Images were captured with a Leica TCS-SP confocal laser scanning microscope equipped with a 63× objective.

Results and discussion

An immobilized GST fusion protein comprising the intracellular C-terminus of mGluR4 (GST-mGluR4-C) was used to isolate interacting proteins from rat brain detergent extracts. Bound proteins were separated by SDS–PAGE and visualized by silver staining (Fig. 1). Protein bands bound only to GST-mGluR4-C but not GST were analyzed by mass spectrometry. This protocol identified ten proteins, most of which were initially found through MALDI-TOF-MS and later confirmed by MALDI-TOF/TOF-MS (Table 1). Two bands at 350 and 270 kDa corresponded to microtubule-associated proteins 1A and 1B (MAP1A and MAP1B). Other proteins linked to the cytoskeleton included spectrin-β2, non-muscle myosin and the cytoskeleton-associated protein 5. Bands of 200 kDa and 100 kDa represented clathrin and the adaptor complex protein AP-2, respectively, e.g. proteins involved in endocytosis. The stable tubule-only polypeptide (STOP) protein was found only once in MALDI-TOF-MS, but is included here because it also was detected by immunoblotting after GST-mGluR4-C pull-down (data not shown).

As in seven independent experiments MAP1B was the most frequently found mGluR4-C binding protein, we confirmed its interaction with mGluR4 by both Western blot analysis and co-immunoprecipitation. In the protein fraction isolated with GST-mGluR4-C but not GST, MAP1B immunoreactivity was enriched as compared to the supernatant (Fig. 2A). Hence, the mGluR4-C sequence specifically binds MAP1B. Furthermore, sequential incubation of brain detergent extracts prepared from wild-type and mGluR4 −/− mice with anti-MAP1B and protein G-agarose produced a 200 kDa (the molecular weight of the mGluR4 dimer; see [4]) mGluR4 immunoreactive band only with wild-type but not mGluR4 −/− samples (Fig. 2B). Thus, endogenous mGluR4 binds endogenous MAP1B in mouse brain extracts.

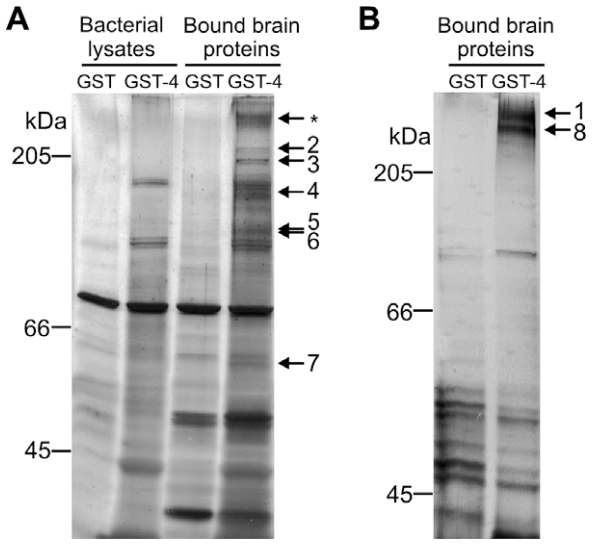

Fig. 1. Identification of proteins binding to GST-mGluR4-C. (A) Rat brain proteins bound to GST-mGluR4-C (GST-4) were separated by 8% SDS–PAGE followed by silver staining. For comparison, rat brain proteins bound to GST alone and the bacterial lysates containing overexpressed GST-mGluR4-C or GST were also analyzed. Arrows indicate bands specifically isolated with GST-mGluR4-C that were analyzed by MS (see Table 1). The asterisk shows a double band further resolved in (B). Positions of molecular-weight markers (in kDa) are indicated. (B) As (A), right lanes, but separation by 6% SDS–PAGE for better resolution of high molecular-weight proteins.

Different proteins have been shown to interact with the C-tails of all group III mGluR family members [3,6]. We therefore examined whether MAP1B binds selectively to mGluR4 or also to other closely related mGluRs. GST pull-down experiments with the intracellular C-terminal domains of mGluRs 6, 7a, 7b, 8a, and 8b showed that all these group III mGluRs bind MAP1B (Fig. 3A). In contrast, no interaction was found with the group II mGluRs 2 and 3 (Fig. 3B).

To localize the MAP1B binding site within the C-terminal domain of group III mGluRs, GST fusion proteins comprising the following peptidic sequences were used in binding assays with detergent extracts from rat brain: the very C-terminal regions of mGluR7a (C27, 27 amino acids) and mGluR8a (C44, 44 amino acids); and the complementary membrane-proximal fragments (N38, 38 amino acids of mGluR7a; and N24, 24 amino acids of mGluR8a) (Fig. 3C). Only the latter gave strong positive binding signals. Comparison of their sequences indicates that the MAP1B binding sites of mGluR7 and mGluR8 reside within a highly conserved 24 amino acid stretch located at the N-terminal regions of the group III mGluR-C tails.

CaM is known to interact with group III mGluRs in a Ca^{2+}-dependent manner [3,4]. The interaction site of Ca^{2+}/CaM lies within the same C-terminal sequence shown above to bind MAP1B. We therefore investigated whether the interaction of MAP1B with GST-mGluR4-C is affected by Ca^{2+}/CaM. In GST pull-down experiments with brain extracts, exogenously added CaM almost completely

Table 1
Proteins identified as candidate mGluR4 interacting proteins.

No.	Protein name (abbreviation)	NCBI Accession No.	MW (kDa)	Score MS	Score MS/MS
1	Microtubule-associated protein 1A (MAP1A)	GI/13591886	350	97	63
2	Myosin, heavy polypeptide 10, non-muscle	GI/13928704	229	246	62
3	Cytoskeleton-associated protein 5 (CAP5)	GI/149022635	189	246	81
4	Spectrin-β2	GI/61557085	160	175	161
5	Adaptor protein complex AP-2	GI/149056010	108	158	77
6	Stable tubule-only polypeptide (STOP) protein	GI/8850229	100	92	
7	Eukaryotic translation factor 2, subunit 3	GI/34880581	52	87	
8	Microtubule-associated protein 1B (MAP1B)	GI/149059171	269	144	91
9	Clathrin (heavy chain)	GI/9506497	191	117	
10	Drebrin 1	GI/13591936	73	117	69

The table lists the names and NCBI accession numbers of the proteins found and the MASCOT scores obtained. MASCOT scores are averaged for the three best measurements for MS (two best scores, if protein was found only twice), and for all experiments in case of MS/MS. MASCOT scores higher than 67 (for MS), or 49 (for MS/MS), were considered significant ($p < 0.05$). Numbers correspond to the gel positions shown in Fig. 1.

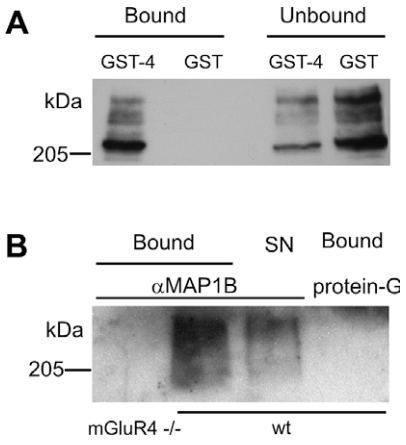

Fig. 2. Verification of MAP1B binding to mGluR4-C. (A) Rat brain proteins bound to GST-mGluR4-C (GST-4), or GST, were separated by 8% SDS–PAGE and analyzed by immunoblotting with anti-MAP1B. MAP1B was co-isolated only with GST-mGluR4-C. Upon incubation with GST, all MAP1B immunoreactivity was found in the unbound protein fraction, while GST-mGluR4-C reduced the amount of MAP1B in this fraction. (B) Co-immunoprecipitation of mGluR4 with MAP1B. Brain extracts prepared from wild-type (wt) or mGluR4 −/− mice were incubated with or without anti-MAP1B followed by protein G-agarose. Bound proteins were analyzed by 8% SDS–PAGE followed by Western blotting with mGluR4 antibody. Only upon inclusion of anti-MAP1B mGluR4 was immunoprecipitated from wild-type extracts; no mGluR4 signal was obtained with MAP1 immunoprecipitates from mGluR4 −/− mice. SN, supernatant containing unbound proteins.

abolished binding of MAP1B to GST-mGluR4-C in the presence of Ca^{2+} but not EGTA (Fig. 3D). Notably, even in the absence of exogenous CaM the binding of MAP1B was strongly decreased by Ca^{2+}. This most likely reflects binding of endogenous CaM in the presence of Ca^{2+}. We conclude that Ca^{2+}/CaM competes effectively with MAP1B for mGluR4 interaction.

The cellular localization of mGluR4 was studied by double immunolabeling in cultured hippocampal neurons. mGluR4 immunoreactivity was found in cell somata, neurites and punctate structures distributed along the latter (Fig. 4A). A similar punctate staining was observed for the presynaptic marker protein vGluT1, which was detected at >80% of the mGluR4-positive puncta (Fig. 4A). Immunolabelling of hippocampal neurons from mGluR4-deficient mice confirmed the specificity of mGluR4 immunoreactivity (Fig. 4A). These results are consistent with mGluR4 being localized in glutamatergic nerve terminals.

Immunostaining of hippocampal neurons with anti-MAP1B revealed a diffuse distribution throughout neurites (Fig 4B). This is in agreement with MAP1B being associated with the microtubular cytoskeleton [19]. In addition, punctate MAP1B signals were

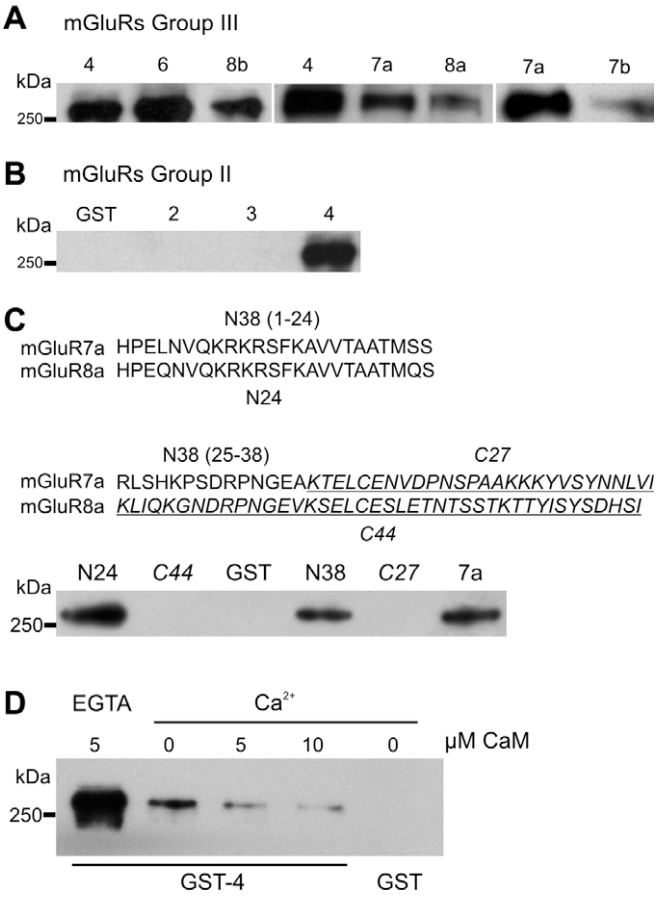

Fig. 3. MAP1B binds to the membrane-proximal tail region of group III mGluRs. GST fusion proteins comprising the C-tails of all group II and group III mGluRs were used for binding assays with rat brain extracts. Bound protein fractions were analyzed by 8% SDS–PAGE and immunoblotting with MAP1B antibody. (A) All group III mGluRC-tails (4, 6, 7a, 7b, 8a, and 8b) interacted with MAP1B. (B) The C-tails of group II mGluRs 2 and 3 did not bind MAP1B. Binding of MAP1B to GST-mGluR4-C is shown as positive control. (C) Mapping of the MAP1B binding region within the group III mGluR intracellular sequence. GST fusion proteins corresponding to the indicated N- or C-terminal truncations of mGluR7a-C and mGluR8a-C were used in a pull-down assay. Note that MAP1B binding was detected only with the respective N-terminal sequences of both receptors. (D) Ca^{2+}/CaM competes with MAP1B for binding to mGluR4-C. Proteins bound to GST-mGluR4-C (GST-4) in the presence of either 5 mM EGTA or 1 mM Ca^{2+} and the indicated concentrations of CaM were analyzed by immunoblotting for MAP1B. In the presence of Ca^{2+}, exogenously added CaM strongly decreased MAP1B binding. In the presence of 5 mM EGTA, MAP1B binding was strongly enhanced, probably due to dissociation of endogenous Ca^{2+}/CaM.

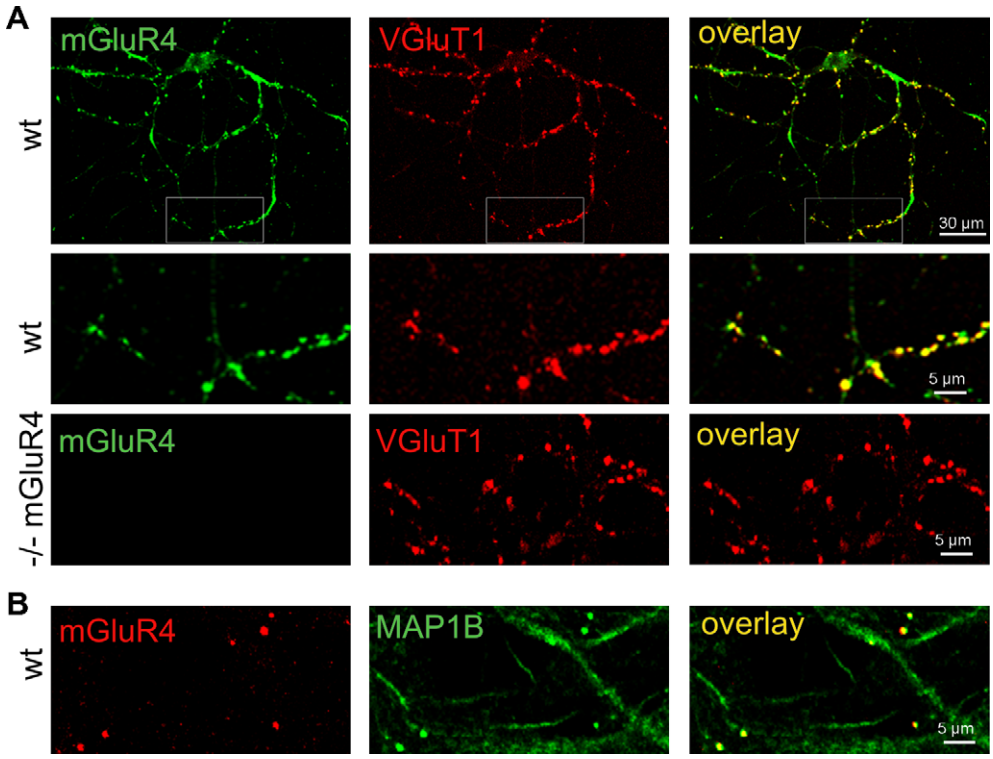

Fig. 4. MAP1B colocalizes with mGluR4 in cultured hippocampal neurons. (A) Upper panels (overviews and blow-ups): Punctate mGluR4 immunoreactivity in dissociated hippocampal neurons cultured for 28 days colocalizes to a large extent with vGluT1 staining. Lower panels: Lack of mGluR4, but not vGluT1, immunostaining in hippocampal cultures prepared from mGluR4 −/− mice. (B) The MAP1B antibody reveals diffuse staining in neurites as well as punctate structures. Many of the latter are mGluR4 positive (see overlay).

observed along the neuritic network. In three independent experiments, 56% of these mGluR4-positive puncta (n = 200) were found to be MAP1B immunoreactive. Thus, endogenous MAP1B and mGluR4 colocalize at synaptic sites of differentiated cultured hippocampal neurons. This is consistent with interactions between these proteins existing *in vivo*.

Together the data presented above allow two major conclusions. First, the proteomic approach used here, GST-mGluR4-C pull-down combined with mass spectrometry, is suitable for identifying novel candidate mGluR4 interacting proteins. Second, MAP1B is a bona fide mGluR4 interaction partner at excitatory synapses. Notably, most of the group III mGluR binding proteins identified previously by yeast two-hybrid screening were not found in our study. This underlines that multiple strategies have to be used for unraveling the full complement of mGluR interactions.

MAP1B plays a major role in the stabilization of microtubules and is also involved in a wide range of cellular functions, such as neuritogenesis and regeneration [20]. Although highly expressed during brain development, MAP1B is found at adult stages and has been implicated in aging and degeneration [19]. In addition to tubulin, MAP1B binds a number of other proteins, such as gigaxonin [21] and the myelin-associated protein MAG [22]. Interestingly, the glutamate receptor-interacting protein GRIP has been reported to bind both MAP1B [23] and mGluR4 [24], suggesting that mGluR4 and MAP1B might interact via GRIP or other mGluR-associated adaptor proteins. The data presented above are consistent with direct binding of MAP1B to mGluR4; however, an indirect interaction cannot presently be excluded. A recent proteomic study aiming at identifying new interaction partners of MAP1B [25] revealed spectrin and clathrin, two proteins also found here as candidate mGluR4 interacting proteins. It is tempting to speculate that we identified these proteins because they belong to synaptic protein complexes involving MAP1B and mGluR4. Interestingly, MAP1B has been reported to interact in brain with an erythropoietin induced GPCR named ee3 [26]. To our knowledge, this is the only other example of an interaction between the C-terminal tail region of a GPCR and MAP1B known to date.

What may be the function of mGluR4–MAP1B interactions? MAP1B binding to ionotropic GABA-C receptors has been implicated in the synaptic clustering of these receptors [27]. However, in MAP1B-deficient mice GABA-C receptors are localized at synapses [28]. Selective agonist stimulation of presynaptic group I mGluRs has been shown to reduce synaptic efficacy by enhancing AMPA receptor endocytosis and increasing MAP1B levels [29], with siRNA inhibition of MAP1B expression blocking receptor internalization [30]. By analogy, group III mGluRs might regulate the trafficking and/or endocytosis of presynaptic receptors via MAP1B. In addition, MAP1B might modulate signal transduction by competing with other interacting proteins for mGluR-C binding.

Acknowledgments

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