Identification and Investigation of *Drosophila* Postsynaptic Density Homologs

Faith L.W. Liebl\(^1\) and David E. Featherstone\(^2\)

\(^1\)Southern Illinois University Edwardsville, Department of Biological Sciences, Edwardsville, IL, U.S.A.
\(^2\)University of Illinois at Chicago, Department of Biological Sciences, Chicago, IL, U.S.A.

**Abstract:** AMPA receptors are responsible for fast excitatory transmission in the CNS and the trafficking of these receptors has been implicated in LTP and learning and memory. These receptors reside in the postsynaptic density, a network of proteins that links the receptors to downstream signaling components and to the neuronal cytoskeleton. To determine whether the fruit fly, *Drosophila melanogaster*, possesses a similar array of proteins as are found at the mammalian PSD, we identified *Drosophila* homologs of 95.8% of mammalian PSD proteins. We investigated, for the first time, the role of one of these PSD proteins, *Pod1* in GluR cluster formation at the *Drosophila* neuromuscular junction and found that mutations in *pod1* resulted in a specific loss of A-type receptors at the synapse.

**Introduction**

The majority of neurotransmission in the mammalian central nervous system uses glutamate as a neurotransmitter. One type of ionotropic glutamate receptor, AMPA receptors (AMPARs), is responsible for fast excitatory transmission in the CNS. The regulated delivery and insertion of AMPARs receptors has been implicated in long term potentiation (LTP, for review see Malinow and Malenka, 2002) and contextual fear learning (Hu et al. 2007; Matsuo et al. 2008). Therefore, the mechanisms that govern AMPAR expression and trafficking are of considerable interest.

AMPARs are tetramers composed of GluR1-4 (Hollmann and Heinemann, 1994; Monaghan and Wenthold, 1997; Gereau and Swanson, 2008). Although AMPARs may be synthesized in dendrites (Ju et al. 2004), most AMPAR mRNA is located in the neuronal cell body suggesting that AMPARs must be transported to their synaptic destinations (Esteban, 2003). There is some evidence that kinesins mediate the cellular trafficking of AMPAR-containing vesicles along the microtubule cytoskeleton. The heavy chain of kinesin directly interacts with GRIP (Setou et al. 2002), which binds to the AMPAR subunits GluR2 and GluR3 (Dong et al. 1997; Srivastava et al. 1998). GluR2 and GRIP also associate with liprin-α (Wyszynski et al. 2002), which interacts with KIF1 (Shin et al. 2003). Vesicles containing AMPARs must be transferred from microtubules to actin filaments before their final delivery into dendritic spines. This process may be mediated by the motor protein, myosin Vb (Lise et al. 2006). Trafficking of receptors to the synapse is mediated by a family of transmembrane regulator proteins (TARPs) (Tomita et al. 2003; Tomita et al. 2004; Tomita et al. 2005; Nicoll et al. 2006; Ziff, 2007) that may also influence AMPAR kinetics (Milstein et al. 2007).

AMPARs are dynamically regulated at the synapse. For example, transient stimulation of NMDA receptors sufficient to produce LTP results in the rapid insertion of AMPARs into the postsynaptic membrane (Liao et al. 1995; Liao et al. 1999; Liao et al. 2001; Poncer and Malinow, 2001) possibly from recycling endosomes (Park et al. 2004). This *de novo* insertion of receptors is dependent upon the interaction between the AMPAR subunit, GluR1 and the scaffolding protein, SAP97 (Hayashi et al. 2000). At synapses, AMPARs are part of dense protein networks called postsynaptic densities (PSD), which are located opposite from presynaptic release sites. The molecular composition of the PSD has been characterized using biochemical approaches, mass spectrometry, and proteomics (Kennedy, 1998; Husi and Grant, 2001; Jordan et al. 2004; Peng et al. 2004; Boeckers, 2006; Collins et al. 2006; Dosemeci et al. 2007) revealing a complex structure composed of hundreds of proteins. The complexity of the interactions between proteins suggests that perturbations of many PSD proteins could affect AMPAR trafficking or localization.
We sought to determine whether the fruit fly, *Drosophila melanogaster*, possesses a similar array of proteins as are found at the mammalian glutamatergic PSD. The *Drosophila* genome encodes 21 putative ionotropic glutamate receptor subunits, including homologs of mammalian NMDA, AMPA, kainate, and delta receptor subunits (Sprengel et al. 2001). The *Drosophila* neuromuscular junction (NMJ) is glutamatergic making it similar in composition and function to mammalian central synapses (Collins and DiAntonio, 2007). The receptors at the NMJ are classified non-NMDA receptors. Similar to their mammalian homologs, *Drosophila* GluRs are tetramers that contain three essential subunits including GluRIIC (Marrus and DiAntonio, 2004), GluRIID (Featherstone et al. 2005), and GluRIIE (Qin et al. 2005) along with either GluRIIA (Schuster et al. 1991) or GluRIIB (Petersen et al. 1997). These two receptor types, A-type (which contain GluRIIA, -IIC, -IID, and -IIE but not -IIB) or B-type (which contain GluRIIB, -IIC, -IID, and -IIE but not -IIA), are differentially expressed and clustered (Marrus and DiAntonio, 2004; Schmid et al. 2008) and interact with distinct components of postsynaptic density (Chen and Featherstone, 2005; Chen et al. 2005).

As in mammals, *Drosophila* glutamate receptors form postsynaptic tetramers that mediate fast synaptic transmission (DiAntonio, 2006), and NMDA receptors are required for learning (Xia et al. 2005, Lin, 2005; Wu et al. 2007). This suggests that glutamate receptor (GluR) function may be largely conserved, but it remains unknown whether mechanisms of glutamate receptor trafficking and anchoring are also conserved. The use of an evolutionarily simpler system could facilitate the understanding of molecular functions and relationships between proteins involved in GluR trafficking. We found that 95.8% of mammalian PSD proteins have *Drosophila* homologs. We investigated, for the first time, the role of one of these PSD proteins, Pod1, in GluR cluster formation at the NMJ and found that mutations in pod1 resulted in a specific loss of A-type receptors at the synapse.

**Materials and Methods**

**Bioinformatics**

We searched the literature for proteins that regulate AMPAR, KARs, or reside in the PSD. Mammalian protein sequences were extracted from the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). The mammalian sequences used were either mouse, rat, or human. The amino acid sequence obtained was compared with annotated proteins in *Drosophila* using FlyBase's BLAST (http://flybase.bio.indiana.edu/blast/). Gene expression patterns were retrieved from the Berkeley Drosophila Genome Project Expression Pattern database (http://www.fruitfly.org/cgi-bin/ex/insitu.pl).

**Antibodies and immunocytochemistry**

For immunocytochemistry and microscopy, animals were dissected and fixed for 30–60 min in either Bouin’s fixative (when GluR antibodies were used), or 4% paraformaldehyde in PBS (for Pod1 labeling). Third instar larvae were dissected and filament prepaerations were pinned down in Sylgard lined Petri dishes. All dissections were done in *Drosophila* standard saline (135 mM NaCl, 5 mM KCl, 4 mM MgCl, 1.8 mM CaCl, 5 mM TES, 72 mM sucrose) at RT. Mouse monoclonal anti-GluRIIA (Iowa Developmental Studies Hybridoma Bank, Iowa City, IA) was used at 1:100. Rabbit polyclonal anti-GluRIIB and anti-GluRIIC were gifts from Aaron DiAntonio (Washington University, St. Louis, MO) and were used at 1:2000 and 1:5000, respectively. Guinea pig polyclonal anti-Pod1 was a gift from Yuh-Nung Jan (University of California, San Francisco) and was used at 1:1000. Fluorescently conjugated anti-HRP (Jackson Immunoresearch Labs, West Grove, PA) was used at 1:100. Goat anti-rabbit, goat anti-mouse, or goat anti-guinea pig fluorescent (FITC or TRITC) secondary antibodies (Jackson Immunoresearch Labs, West Grove, PA) were used at 1:400. The 6/7 NMJ of abdominal hemisegments A3 or A4 were used for all studies. Confocal images were obtained using an Olympus FV500 laser-scanning confocal microscope. Image analysis and quantification was performed using ImageJ and Adobe Photoshop software.

**Electrophysiology**

All electrophysiology was performed on the ventral body wall muscle 6. Larval recordings were performed on third instar larvae 110–120 hr AEL. Muscle 6 was voltage-clamped at −60 mV. Standard two-electrode voltage clamp techniques were used, as previously described (Liebl et al. 2005). Data were acquired and analyzed using a Gene clamp...
500 amplifier and pClamp9 (Axon Instruments, Union City, CA). All dissections and recordings were done in standard *Drosophila* saline at 19°C.

**Fly stocks**
All animals were raised at 25°C in standard fly vials with corn meal molasses medium. Pod1 stocks were gifts from Yuh-Nung Jan (University of California, San Francisco). Control animals used were *w*1118.

**Data acquisition and statistics**
GluR clusters were measured manually by outlining GluR clusters using NIH Image J software as previously described (Featherstone et al. 2002; Chen and Featherstone, 2005; Chen et al. 2005; Rasse et al. 2005). Total GluR fluorescence was quantified by measuring fluorescence intensity at the synapse and subtracting background/muscle fluorescence intensity using Adobe Photoshop CS2. Statistics were performed using GraphPad Prism (v. 4.01). Statistical comparisons were made using unpaired students t-tests or, for distributions, Kolmogorov-Smirnov tests. Statistical significance in figures is represented as follows: * = p < 0.05, ** = p < 0.001, and *** = p < 0.0001. All error bars represent S.E.M.

**Results**

**Most PSD proteins have *Drosophila* homologs**
To assess the similarity by which mammalian and fly non-NMDA receptors might be trafficked and anchored to the synapse, we searched the literature for proteins that interact with AMPARs or KARs. Of the 40 proteins we found that regulate AMPARs or KARs, 38 (95%) have *Drosophila* homologs (Table 1). If these *Drosophila* homologs function similarly to regulate GluR trafficking and localization at the glutamatergic *Drosophila* NMJ, we would expect them to be expressed in neurons, muscle, or both. Therefore, we used the Berkeley *Drosophila* Genome Project (BDGP) Gene Expression Database (http://www.fruitfly.org/cgi-bin/ex/insitu.pl) to examine the expression patterns of these genes. The expression patterns for 14 of these genes are documented. Of these, 5 are expressed in muscle, 6 are expressed in neurons, 2 are expressed ubiquitously, and one is expressed in other tissue. In other words, of the 15 genes with documented expression patterns, 93% are expressed in tissues consistent with conserved function.

Some mammalian GluRs are embedded within the PSD, a specialized protein network that allows postsynaptic cells to receive information. We extended our search of the literature to include proteins that make up the PSD. Of the 199 proteins we found that are localized to the PSD, 191 (96.0%) have *Drosophila* homologs (Supplemental Table 1). 21 of the *Drosophila* genes are homologous for more than one mammalian PSD protein, consistent with the recent confirmation that families of genes expanded between fly and mouse (Emes et al. 2008). The BDGP has documented the expression pattern for 63 of these genes. Of these, 18 are expressed in muscle, 29 are expressed in neurons, 4 are expressed in both neurons and muscle, 7 are expressed ubiquitously, and 5 are expressed in other tissues. Thus, 92% of *Drosophila* proteins homologous to mammalian PSD proteins are expressed in tissues consistent with conserved function. We conclude from these data that the signaling machinery surrounding *Drosophila* GluRs is likely to be similar to that found in the mammalian PSD.

**Mutations in pod1 reduce GluRIIA cluster sizes**
To test whether one of the *Drosophila* genes listed in Supplemental Table 1 plays a role in GluR cluster formation, we examined the NMJ of pod1 mutants. *pod1* is one of two coronin family members in *Drosophila* and has been shown to crosslink actin and microtubules in cultured S2 cells (Rothenberg et al. 2003). We selected *pod1* for further study because the literature suggests a number of cytoskeletal proteins are part of the PSD (40 of the 199 PSD proteins in Supplemental Table 1) and *pod1* is expressed in both neurons and muscle. We first wanted to confirm that *pod1* is localized to NMJs by examining its immunoreactivity (Fig. 1) and found that Pod1 immunoreactivity (which is eliminated in *pod1* mutants; data not shown) is enriched at the NMJ suggesting Pod1 may function at the NMJ.

To determine whether *pod1* affects GluR cluster formation, we examined GluRs in third instar *pod1* mutants, which are viable until pupal stage
Mutant synapses were examined immunocytochemically using α-horseradish peroxidase (HRP) to label the presynaptic motor neuron and α-GluRIIA to label postsynaptic GluRs (Fig. 2). α-HRP recognizes glycosylation of multiple neuronal proteins (Paschinger et al. 2008). Three mutant alleles were used for this analysis: pod1P$^{GT1}BG02604$ (hereafter referred to as pod1$^{P1}$), pod1$^{Δ17}$, and pod1$^{Δ96}$. pod1$^{P1}$ contains a transposable element inserted approximately 300 bp upstream of pod1. The presence of the transposable element reduced Pod1 immunoreactivity to undetectable levels (see above, data not shown). pod1$^{Δ17}$ and pod1$^{Δ96}$ were generated by imprecise excision of the $P\{GT1\}BG02604$ tranposable element and remove the entire coding sequence of pod1 (Rothenberg et al. 2003). Control animals exhibit distinct GluRIIA immunoreactivity visible as small clusters (green) opposite of the presynaptic motor neuron (magenta; Fig. 2A left panels). Each GluR punctum represents an individual postsynaptic density (Chen and Featherstone, 2005; Rasse et al. 2005; Schmid et al. 2008). GluR cluster area, measured immunocytochemically, is directly proportional to the number of GluRs measured electrophysiologically and independent of
changes in NMJ morphology (Featherstone et al. 2002; Chen and Featherstone, 2005; Rasse et al. 2005; Schmid et al. 2008). All three pod1 mutant alleles exhibited a significant reduction in GluRIIA cluster size (Fig. 2A, B and data not shown; $w^{+/+} = 1.34 \pm 0.07 \mu m^2$, $n = 80$ clusters from 8 animals; $pod^{P1} = 0.79 \pm 0.05 \mu m^2$, $n = 66$ clusters from 7 animals, $p < 0.0001$; $pod^{\Delta 17} = 0.53 \pm 0.04 \mu m^2$, $n = 80$ clusters from 8 animals, $p < 0.0001$; $pod^{\Delta 96} = 0.62 \pm 0.06 \mu m^2$, $n = 70$ clusters from 7 animals, $p < 0.0001$). Measurements of total fluorescence intensity indicated there is a 34% and 36% reduction in GluRIIA immunoreactivity in $pod^{\Delta 17}$ and $pod^{\Delta 96}$ mutant animals, respectively (normalized GluRIIA fluorescence $w^{+/+} = 1.00 \pm 0.16$, $n = 15$; $pod^{P1} = 0.69 \pm 0.08$, $n = 9$, $p = 0.12$; $pod^{\Delta 17} = 0.66 \pm 0.09$, $n = 14$, $p = 0.03$; $pod^{\Delta 96} = 0.64 \pm 0.09$, $n = 9$, $p = 0.04$). These data suggest Pod1 is involved in the expression and/or localization of GluRs.

The Drosophila NMJ contains two receptor types, A-type or B-type, which are differentially expressed and clustered (Marrus and DiAntonio, 2004; Schmid et al. 2008) and interact with distinct components of postsynaptic density (Chen and Featherstone, 2005; Chen et al. 2005). This raises the possibility that mutations in pod1 may affect A-type receptors without affecting B-type receptors. To test this possibility, we examined the NMJ of $pod^{\Delta 17}$ mutants using antibodies against either GluRIIB to label B-type receptors or GluRIIC to label all receptors. $pod^{\Delta 17}$ mutants exhibited no difference in either GluRIIB or GluRIIC cluster sizes (GluRIIB: $w^{+/+} = 0.87 \pm 0.04 \mu m^2$, $n = 90$ clusters from 9 animals; $pod^{\Delta 17} = 0.93 \pm 0.06 \mu m^2$, $n = 90$ clusters from 9 animals, $p = 0.3718$; GluRIIC: $w^{+/+} = 1.52 \pm 0.06 \mu m^2$, $n = 100$ clusters from 10 animals; $pod^{\Delta 17} = 1.47 \pm 0.06 \mu m^2$, $n = 100$ clusters from 10 animals, $p = 0.55$). These data indicate that Pod1 affects A-type but not B-type receptors.

To determine whether the loss of A-type GluRs affects the synaptic function of the NMJ, we performed two-electrode voltage clamp. Muscle 6 was voltage clamped at -60 mV and spontaneous miniature excitatory junction currents (sEJCs) were recorded. The frequency of minis is significantly reduced in pod1 mutant animals (Fig. 2C, D; $w^{+/+} = 2.7 \pm 0.23$ Hz, $n = 10$; $pod^{P1} = 1.34 \pm 0.12$ Hz, $n = 8$, $p = 0.0002$; $pod^{\Delta 17} = 0.95 \pm 0.14$ Hz, $n = 7$, $p < 0.0001$). This reduction may represent changes in presynaptic
function (Rothenberg et al. 2003) as well as minis being lost in baseline noise. Consistent with this and the reduction in GluRIIA staining, sEJC amplitudes are also significantly reduced in pod1 mutants (Fig. 2C; pod1P1 K-S statistic = 0.957, p < 0.0001; pod1Δ17 K-S statistic = 0.977, p < 0.0001). The smaller mini amplitudes taken together with the immunocytochemical data indicate that pod1 mutants contain fewer A-type receptors. In agreement with this, we found that the sEJC decay time was significantly reduced in pod1 mutants (data not shown, \(w_{11}^{118} = 12.20 \pm 0.25 \text{ ms, } n = 10; pod1P1 = 9.96 \pm 0.29 \text{ ms, } n = 8, p < 0.0001; pod1Δ17 = 10.76 \pm 0.25 \text{ ms, } n = 7, p < 0.0001\)).

Shorter decay times are associated with specific loss of A-type, but not B-type GluRs. 
We conclude from these data that pod1 plays a role in the expression or localization of A-type, but not B-type GluRs.

**Discussion**

Synaptic plasticity and memory rely on the trafficking and proper localization of postsynaptic GluRs. Although a number of studies address the subunit-specific trafficking of AMPARs at the synapse (for reviews see Malinow and Malenka, 2002; Derkach, Oh et al. 2007; Greger et al. 2007), relatively little is known about how the receptors get transported to the synapse and anchored in the proper locations. The *Drosophila* genome encodes homologs of mammalian NMDA, AMPA, kainate, and delta receptor subunits (Sprengel et al. 2001). Therefore, an evolutionarily simpler system such as *Drosophila* could be used to dissect the function of genes and proteins that regulate GluR trafficking.

We searched the literature for proteins that regulate AMPARs or KARs and proteins that are found within the PSD. 95.8% of these proteins have *Drosophila* homologs. No homologs were found for 11 mammalian proteins. Interestingly, this included the scaffolding proteins Bassoon (Takao-Rikitsu, 2004) and AKAP 79/150 (Dell-Acqua et al. 2006). This may be due to the reduced complexity of the fly NMJ (see below).

Several lines of evidence suggest these *Drosophila* homologs may have conserved functions. First, of the homologs we examined with documented expression patterns, 92.2% are found in neurons, muscle, or both, consistent with conserved function. Further, 31 of these homologs have been reported at the *Drosophila* NMJ, which is a glutamatergic synapse. Second, 29 of the homologs were recently identified by mass spectrometry as members of a protein complex associated with the *Drosophila* NR2 GluR subunit (Emes et al. 2008).

Third, two of the *Drosophila* homologs have been shown to regulate GluRs. Pak positively regulates GluR cluster formation at the NMJ when it is downstream of Dock (Albin and Davis 2004). Coracle, the *Drosophila* homolog of the mammalian 4.1 N protein (see Table 1), interacts with GluRIIA subunits and anchors A-type receptors to the actin cytoskeleton (Chen et al. 2005). Finally, four of the *Drosophila* homologs, Didum (Myosin Va), l(1)G0003 (Rab11 family interacting protein), Pnut (Cdc10 and Septin 7), and Polo (Polo-like kinase) were identified in a forward genetic screen for genes that regulate GluR cluster formation (Liebl and Featherstone, 2005) at the *Drosophila* NMJ. We present evidence here that indicates that Pod1, the *Drosophila* homolog of Coronin 7 (see Supplemental Table 1), also regulates GluR cluster formation at the *Drosophila* NMJ.

The Coronins are an evolutionarily conserved family of proteins that regulate the actin cytoskeleton and vesicle transport (for reviews see Rybakin and Clemen, 2005; Uetrecht and Bear, 2006). Mammalian Coronins 1a (Collins et al. 2006), 1b, 1c (Peng et al. 2004; Collins et al. 2006), and 2b (Jordan et al. 2004; Collins et al. 2006) were identified as components of the PSD via mass spectrometry. Coronin 7 is localized to the cis-Golgi and cytoplasmic vesicles (Rybakin et al. 2004). There are two *Drosophila* Coronin homologs. Coro is most similar to Coronins 1a, 1b, 1c, and 2b while Pod1 is most similar to Coronin 7. None of these proteins have been previously linked to GluRs. Previous studies in *Drosophila* (Rothenberg et al. 2003; Bharathi et al. 2004) and mammals (Rybakin and Clemen, 2005; Uetrecht and Bear, 2006), however, indicate that the coronins are expressed in the nervous system and/or muscle. This, coupled with their role in cytoskeleton remodeling, suggests they may be involved in GluR cluster formation. Consistent with this, we found Pod1 present at the NMJ (Fig. 1). It has also been shown to be localized in the tips of growing motor neuron axons during embryogenesis in *Drosophila* (Rothenberg et al. 2003).

We tested our hypothesis that Pod1 is involved in GluR cluster formation by examining pod1 mutant synapses. The loss of pod1 led to a reduction in the size of GluRIIA-containing clusters as
Table 1. *Drosophila* glutamate receptor-associated protein homologs.

| Protein                                      | Accession number | Proposed function                                                                 | Drosophila homolog | % Identity/positives |
|----------------------------------------------|------------------|-----------------------------------------------------------------------------------|--------------------|----------------------|
| 4.1 N                                        | Q9H4G0           | May provide a link between AMPARs and the cytoskeleton by binding to GluR1 (Shen et al. 2000) | Cora               | 57.8/73.5            |
| AMPAR Binding Protein                        | AF090113.1       | Protein scaffold that binds to the PDZ domain of GluR2 (Srivastava and Ziff, 1999) | GRIP               | 30.9/49.0            |
| AKAP 79/150                                  | NM_133515.1      | Anchor kinases and phosphatases and binds to SAP97 (Colledge et al. 2000)         | None               |                      |
| Adenomatous polyposis coli (APC)             | NM_000038.3      | Involved in AMPAR clustering possibly by its interaction with PSD-95 (Senda et al. 2005; Shimomura et al. 2007) | APC                | 53.1/63.5            |
| AP-2, μ2                                     | NM_001025205.1   | Binds to cytoplasmic tail of AMPARs to promote endocytosis of receptors (Osterweil et al. 2005; Kastning et al. 2007) | AP-50              | 87.2/94.3            |
| Actinfilin                                   | NM_145671.1      | Targets KARs for degradation by binding to both GluR6 and Cullin 3 (Salinas et al. 2006) | CG15097            | 54.4/71.4            |
| β-catenin                                    | NM_007614.2      | Forms a complex with N-cadherin and AMPARs possibly regulating surface expression of AMPARs (Nuriya and Huganir, 2006) | Arm                | 66.3/76.7            |
| cGMP-dependent protein kinase II (cGKII)     | Z36276.1         | Increases extrasynaptic surface expression of AMPARs by binding to GluR1 CTD (Serulle et al. 2007) | For Pkg21D         | 50.2/68.7            |
| Dynamin-3                                    | NM_015569.2      | Maintains level of synaptic AMPARs by positioning endocytic proteins near the PSD (Lu et al. 2007) | Shi                | 69.6/81.9            |
| GIT-1                                        | Q9Z272           | Involved in AMPAR trafficking by forming a complex with AMPARs, KIF1A, GRIP, and liprin-α (Shin et al. 2003; Lu et al. 2007) | CG16728            | 44.1/59.2            |
| GRIP-associated protein 1 (GRASP-1)          | NM_207672.1      | RasGEF that binds to GRIP and JNK and regulates synaptic targeting of AMPARs (Ye et al. 2000; Ye et al. 2007) | CG31784            | 25.2/47.3            |

(Continued)
| Protein | Accession number | Proposed function                                                                 | Drosophila homolog | % Identity/positives |
|---------|------------------|-----------------------------------------------------------------------------------|--------------------|----------------------|
| GRIP    | NM_021150.1      | Scaffolding protein that binds to GluR2 and GluR3 (Dong et al. 1997)             | GRIP               | 56.1/81.7            |
| Hsp90   | S45392.1         | Required for constitutive cycling of AMPARs (Gerges et al. 2004b)                | Hsp83              | 70.7/79.7            |
| JNK     | AB005665.1       | Acts on GluR2 (long isoform) and GluR4 to regulate cell surface expression of AMPARs (Zhu et al. 2005; Thomas et al. 2008) | Bsk                 | 77.7/87.2            |
| KIF1A   | Q12756           | Involved in AMPAR trafficking by forming a complex with AMPARs, GIT-1, GRIP, and liprin-α (Shin et al. 2003; Lu et al. 2007) | Unc-104            | 55.2/68.7            |
| KIF17   | AB001424.1       | Required for localization of KARs by binding to GluR6 and KA2 (Kayadjanian et al. 2007) | Klp64D             | 57.5/71.2            |
| Kalirin | NM_032062.1      | RhoGEF that interacts with GluR1 and regulates AMPAR insertion in response to activity (Xie et al. 2007) | Trio               | 41.6/60.7            |
| KRIP6   | Q56A24           | Regulates KARs by binding to GluR6 (Laezza et al. 2007)                          | Dbo                | 35.9/50.6            |
| Lin-10  | NM_025187.3      | Involved in AMPAR trafficking by binding to PDZ domain (Stricker and Huganir, 2003) | CG7083             | 51.9/67.9            |
| Liprin-α| BC034046.1       | Involved in AMPAR trafficking by forming a complex with AMPARs, KIF1A, GIT-1, and GRIP (Shin et al. 2003; Lu et al. 2007) | Liprin-α           | 47.8/60.2            |
| Myosin Va | NM_000259.2    | Required for transport of AMPARs during synaptic activity (Correia et al. 2008)  | Didum              | 39.5/57.6            |
| Myosin Vb | NM_001080467.1  | Regulates AMPAR surface expression by associating with GluR1 (Lise et al. 2006) | Didum              | 42.8/60.3            |
| Myosin VI | NM_004999.3     | Involved in AMPAR endocytosis (Osterweil et al. 2005) and forms a complex with GluR1 and SAP-97 (Wu et al. 2002) | Jar                | 53.2/71.5            |
| Protein                                           | Accession number | Proposed function                                                                                                                                                                                                 | Drosophila homolog | % Identity/positives |
|--------------------------------------------------|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|---------------------|
| N-cadherin                                       | AB017695.1       | Forms a complex with neural plakophilin-related arm protein (NPRAP), ABP, and GRIP to anchor AMPARs (Silverman et al. 2007)                                                                                     | CadN              | 29.0/44.4           |
| Neuronal-activity related pentraxin (NARP)       | S82649.1         | Associate with GluR1-containing AMPARs and may play a role in clustering of AMPARs (O’Brien et al. 1999; O’Brien et al. 2002)                                                                                        | B6                | 29.9/46.2           |
| NEEP21                                           | NM_024128.3      | Component of neuronal endosomes that is necessary for the recycling of AMPARs (Steiner et al. 2005; Kulangara et al. 2007)                                                                                      | None              |                    |
| NPRAP                                            | Q9UQB3           | Forms a complex with N-cadherin, ABP, and GRIP to anchor AMPARs (Silverman et al. 2007)                                                                                                                      | P120ctn           | 46.2/62.9           |
| NSF                                              | AL603829.5       | Promotes constitutive cycling of AMPARs (Nishimune et al. 1998) by disrupting GluR2 and PICK1 (Hanley et al. 2002)                                                                                            | Nsf2 Comt         | 60.1/74.4 59.7/74.0 |
| PICK1                                            | AB026491.1       | Promotes internalization of GluR2-containing AMPARs (Perez et al. 2001; Terashima et al. 2004)                                                                                                                  | PICK1             | 60.8/76.3           |
| Rab8                                             | AF498943.1       | Involved in constitutive cycling and delivery of AMPARs to membrane surface (Gerges et al. 2004a; Brown et al. 2007)                                                                                        | Rab8              | 79.2/88.4           |
| Rab11                                            | P62494           | Responsible for delivery of GluR1-containing receptors to the synapse (Park et al. 2004; Brown et al. 2007)                                                                                            | Rab11             | 85.5/90.2           |
| RIL                                              | Y08361.1         | Links internalized GluR1-containing receptors to actin cytoskeleton (Schulz et al. 2004)                                                                                                                    | CG30084           | 41.2/51.0           |
| SAP97                                            | NM_012788.1      | Scaffolding protein that binds to GluR1 (Leonard et al. 1998)                                                                                                                                               | Dlg1              | 53.9/68.6           |
| Shank                                            | AF133301.1       | Scaffolding protein that helps position AMPAR endocytic machinery at the PSD (Lu et al. 2007)                                                                                                                 | Prosap            | 50.6/67.2           |

(Continued)
Table 1. (Continued)

| Protein | Accession number | Proposed function | Drosophila homolog | % Identity/positives |
|---------|------------------|-------------------|--------------------|---------------------|
| SNAP (β isoform) | P28663 | Mediates disassembly of GluR2-PICK1 complex (Hanley et al. 2002) | Snap | 61.6/78.2 |
| SUMO | P63166 | Modifies GluR6 to promote endocytosis of KARs (Martin et al. 2007) | Smt3 | 52.3/70.5 |
| SynGAP | NM_001113409.1 | Involved in AMPAR trafficking to synapse (Rumbaugh et al. 2006) | CG32560 | 37.7/55.1 |
| γ2 (Stargazin) | NM_006078.2 | Involved in localization of AMPARs to synapse and delivery to cell surface (Chen et al. 2000) | Stg1 | 26.1/38.9 |
| γ3 (TARP) | NM_006539.2 | Required for expression of AMPARs on cell surface (Tomita et al. 2003) | Stg1 | 27.7/42.9 |
| γ8 (TARP) | NM_080696.2 | Required for expression of AMPARs on cell surface (Tomita et al. 2003) | Stg1 | 28.9/43.0 |

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well as a significant reduction in synaptic GluRIIA immunoreactivity. Interestingly, the GluR cluster sizes determined microscopically do not differ between pod1P1 and pod1A17, despite the fact that mini amplitudes in pod1A17 null mutants are much lower. Surface expression of some GluRIA may therefore be supported in pod1P1 mutants even when total synaptic GluRIA is severely reduced. A-type receptors are linked to the actin cytoskeleton via their interaction with coracle (Chen et al. 2005). This raises the possibility that the loss of GluRIA is specific to the synapse. In this scenario, A-type receptors would be trafficked to the synapse but not properly anchored to the synapse in pod1 mutants. Alternatively, pod1 could be required for transport of GluRIA-containing receptors from the cis Golgi to the synapse. Further studies will be required to determine how the loss of pod1 affects A-type receptor trafficking.

There was no significant reduction in the sizes of GluRIIB or GluRIIC clusters. This is likely because B-type receptors are anchored to the cellular cytoskeleton in a different, unknown way. These data are consistent with the role of the coronins in mammals where they are known to regulate the actin cytoskeleton (Cai et al. 2008; for reviews see Rybakin and Clemen, 2005; Uetrecht and Bear, 2006) and suggests Coronin 7 may also participate in actin regulation. Although both A- and B-type receptors at the Drosophila NMJ are linked to microtubules (Liebl et al. 2005), only A-type receptors depend on the integrity of the actin cytoskeleton (Chen et al. 2005).

There exist a number of important differences between mammalian central synapses and Drosophila NMJ synapses. First, the Drosophila NMJ is a single cell in vivo system where a single presynaptic motor neuron synapses on a single postsynaptic muscle cell. It is estimated that mammalian CNS neurons synapse with as many as 10,000 other neurons. Therefore, the Drosophila NMJ is a simple model system lacking the complexity found in mammalian CNS synapses. This could partly account for the small percentage of mammalian proteins with no Drosophila homologs. Second, because the postsynaptic cell at the NMJ is a muscle cell, Drosophila NMJs lack dendritic spines but extend filopodia to contact presynaptic
motor neurons during embryonic development (Ritzenthaler et al. 2000; Ritzenthaler et al. 2003). Thus, proteins and mechanisms specific to dendritic spines are probably not included at the fly NMJ. The NMJ, however, represents only a small percentage of fly glutamatergic synapses. Most fly glutamatergic synapses are found in the larval and adult CNS (Daniels et al. 2008). Consistent with this, many of the putative fly PSD proteins identified here are expressed in the fly CNS. Glutamate receptors and PSD proteins in the fly CNS probably function as in mammals. For example, similar to mammalian studies, central NMRA receptors are required for fly learning (Glanzman, 2005; Lin, 2005; Xia et al. 2005; Wu et al. 2007). It is currently unknown whether fly central synapses exhibit plasticity, but the NMJ exhibits post tetanic potentiation (Kuromi and Kidokoro, 2003; Cheung et al. 2006) and LTD (Guo and Zhong, 2006).

In conclusion, we have shown that most mammalian PSD proteins have Drosophila homologs and that these homologs are likely to have conserved functions. Therefore, the analysis of mutant phenotypes in Drosophila could enhance our understanding of GluR cluster formation and the PSD. Consistent with this, we have shown for the first time that the Drosophila homolog of Coronin 7, Pod1, is involved in the formation of GluRIIA containing GluR clusters possibly by regulating the actin cytoskeleton.

Acknowledgements
We thank the Iowa Developmental Hybridoma Bank, the Aaron DiAntonio lab, and Yuh-Nung Jan lab for antibodies and the Bloomington Stock Center for fly stocks. This work was supported by an NIH grant to D.F., an NIH Academic Research Enhancement Award (1R15NS063315–01) to F.L., and a Summer Research Fellowship from Southern Illinois University Edwardsville.

Abbreviations
BDGP, Berkeley Drosophila Genome Project; GluRs, glutamate receptors; HRP, horseradish peroxidase; LTD, long term depression; LTP, long term potentiation; NMDA, N-methyl-D-aspartate; NMJ, neuromuscular junction; PSD, postsynaptic density; TARPs, transmembrane AMPA receptor regulatory proteins; KARs, kainate receptors.

Disclosure
The authors report no conflicts of interest.

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