Arcadlin Is a Neural Activity-regulated Cadherin Involved in Long Term Potentiation*

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Kanato Yamagata†‡, Katrin I. Andreasson†, Hiroko Sugii†, Eiichi Maruji, Muller Dominique**
Yasuyuki Irie‡‡, Naomasa Miki‡‡, Yokichi Hayashi§§, Masatomo Yoshioka¶¶, Kenya Kaneko¶¶,
Hiroshi Kato§§, and Paul F. Worley¶¶

From the †Department of Molecular Neurobiology, Tokyo Metropolitan Institute for Neuroscience, Fuchu 183, Japan, the §Department of Neuroscience and Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, the ¶Department of Physiology II, Nippon Medical University School of Medicine, Tokyo 113, Japan, the **Department of Pharmacology, Centre Medical Universitaire, CH-1211 Geneve 4, Switzerland, the ¶¶Department of Pharmacology I, Osaka University School of Medicine, Suita 565, Japan, §§Nagano Nursing University, Komagane 399-41, Japan, and the ¶¶¶Department of Physiology II, Yamagata University School of Medicine, Yamagata 990-23, Japan

Neural activity results in long term changes that underlie synaptic plasticity. To examine the molecular basis of activity-dependent plasticity, we have used differential cloning techniques to identify genes that are rapidly induced in brain neurons by synaptic activity. Here, we identify a novel cadherin molecule Arcadlin (activity-regulated cadherin-like protein). Arcadlin mRNA is rapidly and transiently induced in hippocampal granule cells by seizures and by N-methyl-D-aspartate-dependent synaptic activity in long term potentiation. The extracellular domain of Arcadlin is most homologous to protocadherin-8; however, the cytoplasmic region is distinct from that of any cadherin family member. Arcadlin protein is expressed at the synapses and shows a homophilic binding activity in a Ca^{2+}-dependent manner. Furthermore, application of Arcadlin antibody reduces excitatory postsynaptic potential amplitude and blocks long term potentiation in hippocampal slices. Its close homology with cadherins, its rapid inducibility by neural activity, and its involvement in synaptic transmission suggest that Arcadlin may play an important role in activity-induced synaptic reorganization underlying long term memory.

Glutamate receptor stimulation leads to a rapid Ca^{2+} influx into neurons with associated protein phosphorylation events that underlie short term memory. In contrast, long term memory can be distinguished from short term memory in that it requires new mRNA and protein synthesis (1). To analyze components of the gene expression program underlying long term memory in the vertebrate brain, we and others have employed differential cloning techniques to identify mRNAs that are rapidly induced by excitatory activity. In addition to transcription factors, this approach has identified a number of immediate early genes that encode enzymes that may directly modify cellular function, including tissue-plasminogen activator, cyclooxygenase-2, a novel small molecular weight G-protein, and a cytokine-activated protein (2–6). These proteins presumably interact with neuronal proteins and indirectly affect long term changes in connections and the efficacy thereof. LTP provides a widely adopted mammalian model for activity-dependent changes in synaptic efficacy. The mechanisms contributing to long term changes in synaptic transmission are still contentious. Among many possibilities, one of the hypotheses that has been proposed is that neural activity could lead to modifications in synaptic structure and eventually changes in synaptic connectivity. In support of this idea, numerous morphological studies have provided evidence that neural activity such as kindling or electrical stimulation induces modifications in dendritic arborization, spine densities, or synaptic morphology (7–10).

Adhesion molecules are known to be involved in many aspects of cell-cell interactions, including cell migration, axonal growth, pathfinding, sprouting, and regeneration (11, 12). Recent reports have demonstrated that some adhesion molecules are expressed at the synapses and are involved in synaptic transmission. Kandel and colleagues (13) demonstrated that a cell adhesion molecule (apCAM) contributes to synaptic plasticity. In addition, studies using antibodies that interfere with the binding of L1 and the neural cell adhesion molecule (NCAM) have shown that these molecules are required for LTP induction in the hippocampus (14, 15).

Here we describe a novel cell adhesion molecule, Arcadlin, whose expression is tightly regulated by synaptic activity in brain neurons. As Arcadlin is a synaptic protein and binds to itself in a Ca^{2+}-dependent manner, we have then asked whether blocking antibody affect synaptic transmission and LTP in hippocampal slices.

EXPERIMENTAL PROCEDURES

Construction and Screening of a Subtracted Library—A subtracted cDNA library was constructed as described (3). It was screened with 32P-labeled cDNA prepared by reverse transcription of poly(A)+ RNA prepared from the hippocampus of control or seizure stimulated rats. Nearly full-length cDNAs and a genomic DNA clone of rat arcadlin were isolated by screening an unsubtracted, oligo(dT)-primed cDNA library and a rat genomic library, respectively.
Northern Analysis—This procedure was performed as described previously (16) with 20 \( mg \) of total RNA/lane. The probe used for Northern analysis was 1.0-kilobase pair 3'-end fragment of arcadlin cDNA. The cDNA fragment was labeled by the random priming technique using \([\alpha-^{32}P]dCTP.\]

In Situ Hybridization—Control and experimental tissues were frozen in the same tissue block to ensure identical conditions during tissue sectioning, subsequent storage, and in situ hybridization. \( 35S- \) and digoxigenin-labeled arcadlin antisense riboprobes were prepared from an appropriately restricted plasmid containing the near full-length cDNA. In situ hybridization was performed as described previously (17).

Electrophysiology—Seizures were induced in adult male Wistar rats by maximal electro-convulsive seizure (MECS) using a constant-current signal generator (ECT Unit, UgoBasil, Italy) as described previously (18). For in vivo LTP studies, rats were implanted bilaterally with stimulating and recording electrodes in the perforant path and the hilus of the dentate gyrus as described previously (19). For in vitro LTP studies, hippocampal slices (500 \( \mu m \)) were prepared from rats (100–200 days old).

**FIG. 1.** Nucleotide sequence of rat arcadlin cDNA and its predicted amino acid sequence. Numbering for nucleotides, on the right, is from a translation start site. Two independent cDNAs were sequenced on opposite strands and yielded identical sequences. Filled triangle shows the position where 293-base pair exon is inserted in human pcdh8 cDNA.
A Neural Activity-regulated Cadherin

**FIG. 2.** Comparison of the deduced amino acid sequences of rat Arcadlin (r-Arcd) and human protocadherin 8 (h-Pcdh8). Conserved amino acids between Arcadlin and protocadherin-8 are boxed. EC1–EC6 indicate cadherin repeats in the extracellular domains. The putative signal peptide sequence and transmembrane segment are indicated by thin and thick lines, respectively.

Antisera Preparation—Anti-Arcadlin rabbit polyclonal antisera were generated using either the extracellular (amino acids 31–730) or cytoplasmic domain. A nitrocellulose filter strip of 2 cm² was dissolved in 4.8 ml of methanol and dried onto test dishes. Aliquots (0.1 ml) of test sample containing either 100 ng/ml BSA or control IgG, the cell suspension was incubated with antibody at a final concentration of 0.2 mg/ml on ice for 30 min. Plated cells were incubated at 37 °C for 2 h, then washed four times with PBS(−), and fixed with 4% paraformaldehyde solution. Adhesion to the dishes was assayed by phase-contrast microscopy.

Immunohistochemistry—Eight-week-old rats were anesthetized and perfused with 4% paraformaldehyde. Whole brains were removed and immunoperoxidase staining was performed with a Vectastain Elite ABC kit. Primary hippocampal cultures were prepared from embryonic day 18 rat embryos as described (22). Cells were fixed in 4% paraformaldehyde for 1 h, permeabilized with 0.1% Triton, and stained with anti-Arcadlin antiserum and anti-synaptophysin monoclonal antibody. Anti-Arcadlin and synaptophysin were detected by fluorescein isothiocyanate-conjugated anti-rabbit and rhodamine-conjugated anti-mouse antibodies, respectively.

**RESULTS**

Cloning of Rat Arcadlin cDNA—Differential and subtractive cloning techniques were used to identify mRNAs that were rapidly induced in the hippocampus by seizures. A novel cDNA corresponding to the 3’-noncoding region of an mRNA of about 4.5 kilobase was isolated. Nearly full-length cDNAs were then isolated by screening a seizure-stimulated rat hippocampal cDNA library. The nucleotide sequence encompassed the entire putative coding sequence that predicted a 972-amino acid protein, Arcadlin as a glutathione S-transferase fusion. Both antisera detect a seizure-inducible 110-kDa protein in the hippocampus. For electrophysiological experiments, pre-immune and antisera against EC domain were purified with Protein A-Sepharose.

Cell Adhesion Assay—Cell adhesion experiments were carried out according to the method of Lemmon et al. (21). A nitrocellulose filter strip of 2 cm² was dissolved in 4.8 ml of methanol and dried onto test dishes. Aliquots (0.1 ml) of test sample containing either 100 ng/ml BSA or the extracellular domain of Arcadlin were plated on the dried surface and incubated for 1 h in a humidified CO₂ incubator at 37 °C. The cells were collected, dissociated by gentle pipetting, and suspended in Dulbecco’s modified Eagle’s medium containing 10% fetal calf serum at 2 × 10⁶ cells/ml. The cells were kept on ice to inhibit aggregation. Aliquots of the cell suspension were placed on the test dishes with or without 1 mM Ca²⁺. To assess inhibition of adhesion by antibodies, the cell suspension was incubated with antibody at a final concentration of 0.2 mg/ml on ice for 30 min. Plated cells were incubated at 37 °C for 2 h, then washed four times with PBS(−), and fixed with 4% paraformaldehyde solution. Adhesion to the dishes was assayed by phase-contrast microscopy.

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recognizable homology in the GenBank data base and is distinct from that of Pcdh8, because rat arcadlin cDNAs lacked a 293-base pair exon coding the cytoplasmic region of Pcdh8 (Fig. 1). To ascertain whether arcadlin is a real splice variant of rat pcdh8, we tried to isolate a pcdh8-type cDNA from the rat library; however, we failed to find any clone with this exon. All 62 clones we isolated from the rat library coded the identical cytoplasmic sequence to that of Arcadlin. Therefore, we may say that splicing of rat pcdh8/arcadlin pre-mRNA is different from that of human mRNA, resulting in the synthesis of Arcadlin form with a longer cytoplasmic domain.

Expression and Regulation of arcadlin mRNA—arcadlin mRNA was assayed by Northern blot analysis. arcadlin gene expression is enriched in various regions of the brain (except for the cerebellum) relative to peripheral tissues (Fig. 3c). In the hippocampus, the 4.5-kilobase message is induced within 30 min after MECS, peaks at 2 h, and remains elevated for as long as 8 h (Fig. 3, a and b). Rat presenilin-1 (PS1) mRNA was analyzed with the same blot as a control (Fig. 3, a and b). In situ analysis demonstrated arcadlin mRNA is dramatically increased in granule cells, and modestly induced in the pyramidal cells of the hippocampus after MECS (Fig. 4a). The tetanic stimulus to the perforant pathway also induced arcadlin in the hippocampus and the entorhinal cortex (Fig. 4b), indicating that arcadlin induction occurs in both pre- and postsynaptic neurons during LTP. arcadlin mRNA is also expressed in structures during early development that subserved specific neuronal circuits, specifically the auditory, visual and limbic systems (Fig. 4, c–g). In the auditory circuit, arcadlin mRNA is prominently expressed in the inferior colliculus at embryonic day 17 (Fig. 4c), and later in the medial geniculate and the auditory cortex at P0 (Fig. 4, d–g). At P0, arcadlin is also expressed in targets of retinal projections, such as the superior colliculus, the suprachiasmatic nucleus, and the ventrolateral geniculate nucleus (Fig. 4, f and g). Furthermore, arcadlin mRNA is detected in selected structures of the limbic circuit, including the anterior limbic thalamic nuclei, the hippocampus, amygdala, and habenula (Fig. 4, d–f).

Functional Analysis of Arcadlin Using L Cells—To examine the predicted cadherin-like adhesion properties of Arcadlin, the coding sequence of arcadlin cDNA was introduced into L cells. Cells were then tested for interaction with the extracellular domain of Arcadlin. Arcadlin was applied to nitrocellulose-coated dishes, and cell binding was examined by the method of Lemmon et al. (21) (Fig. 5). In the presence of 1 mM Ca2+, the arcadlin-expressing cells (Fig. 5d), but not the parental L cells (Fig. 5a), adhered to the Arcadlin-coated dishes. In the absence of Ca2+, arcadlin-expressing cells did not bind to the dishes (Fig. 5c). Ca2+-dependent adhesion was blocked by preincubation of the coated dishes with Arcadlin antibody (Fig. 5f), but not with preimmune serum (Fig. 5e). Neither the transfectants nor the parental cells adhered to the control dishes coated with BSA (Fig. 5b). These data are consistent with functional properties of other cadherins and suggest that Arcadlin also possesses Ca2+-dependent homophilic binding activity.

Synaptic Localization of Arcadlin Protein—Immunohistochemical analyses demonstrated that Arcadlin protein is expressed in cell bodies and dendrites of neurons in the hippocampus and cortex in adult rat brain (Fig. 6, a and c). Arcadlin immunostaining in the hippocampus markedly increased 4 h following a seizure with prominent staining of dendrites within the molecular layer (Fig. 6b). Western blot with the same antibody showed an apparent molecular mass of 110 kDa membrane protein is induced after a seizure (Fig. 6d). We also examined Arcadlin immunostaining in primary cultures of hippocampal neurons (Fig. 6e). Arcadlin is naturally expressed in hippocampal neurons and localized at both soma and synapses in association with the marker synaptophysin. These observations confirm that Arcadlin protein is dynamically regulated by neural activity and is localized at synapses.

Arcadlin Antibody Suppresses Synaptic Transmission and Blocks LTP—The Arcadlin antibody provides a tool to investigate the possible role of Arcadlin in the synaptic function of hippocampal neurons using the acute in vitro slice preparation. Arcadlin and control IgGs were infused into the dendritic regions of CA1 or dentate gyrus and f-EPSP was recorded. IgGs were purified with Protein A-Sepharose (Fig. 7a), and they well diffused into the hippocampal tissue (Fig. 7b). A comparison of the effect of Arcadlin and control IgG in the presence of Ca2+-indicated no obvious differences in f-EPSPs or LTPs induced by the tetanic stimulation (data not shown). Based on the premise that Arcadlin may be naturally present in a homophilic bound state in tissue, and therefore resistant to the blocking antibody, we examined the effect of administering the IgGs during a brief period of free Ca2+. As anticipated, synaptic responses in Ca2+-free medium were abolished. Upon restoration of Ca2+, evoked EPSPs in the molecular layer of the dentate gyrus returned to near baseline level in slices that received control IgG but remained significantly reduced in slices treated the Arcadlin IgG (Fig. 7c). Mean recoveries of EPSP were 91.8 ± 2.9% and 59.9 ± 9.3% (mean ± S.E., n = 7, p < 0.01; Fig. 7d) with control and Arcadlin IgGs, respectively. Furthermore, tetanus failed to produce LTP in Arcadlin IgG-injected granule cells (Fig. 7c, n = 5), while it induced LTP in 4 out of 5 slices in control IgG-
treated regions (Fig. 7c, n = 5). Magnitude of LTP recorded from CA1 was suppressed in a dose-dependent manner with Arcadlin IgG and significantly smaller than with control IgG (data not shown). The blocking effect of Arcadlin antibody on LTP is consistent with its partial block of EPSP and suggests that Arcadlin plays an important role in natural synaptic transmission.

DISCUSSION

The cadherin superfamily is a large and extremely diverse group of calcium-dependent, membrane associated glycoproteins. Cadherins are involved in many aspects of cell-cell interactions, including axonal growth, pathfinding, and sprouting (24). Recent studies have demonstrated that some cadherins and catenin are localized in synaptic complexes and function as primary adhesive moieties between pre- and postsynaptic membranes (25, 26). Moreover, Tang et al. demonstrated antibodies to N-cadherin or E-cadherin prevent LTP, suggesting that classical cadherins are involved in synaptic plasticity (27). More than 30 cadherins have been characterized, but so far no member of the family has been shown to be regulated by synaptic activity.

We isolated and characterized a cDNA encoding a novel activity-regulated cadherin family member, termed Arcadlin. arcadlin mRNA is strongly induced in the hippocampus and the entorhinal cortex by non-epileptic, N-methyl-D-aspartate receptor-dependent synaptic stimuli in association with physiological synaptic enhancement. The alignment of the extracellular domain sequences of Arcadlin and Pcdh8 suggests possible common structural features of these domains, as is the case with classical cadherins. arcadlin may be a rat homologue of human pcdh8; however, the cytoplasmic region of Arcadlin is clearly different from that of Pcdh8, because arcadlin cDNA lacked the 293-base pair exon coding the cytoplasmic region of human Pcdh8. Then, we tried to isolate from the rat library a pcdh8-type cDNA; however, we were not able to find any clone with this exon. Furthermore, as the antibody against the cytoplasmic region of Arcadlin recognizes an inducible 110-kDa...
protein (Fig. 6d), it is clear that Arcadlin form really exists and is regulated in the rat brain. Therefore, splicing of rat pcdh8/arcadlin pre-mRNA may be distinct from that of human, resulting in the synthesis of Arcadlin form with a longer cytoplasmic domain.

The cytoplasmic domains of classical cadherins play a key role in the cell-cell interaction through association with catenins. In addition, other adhesion molecules have been shown to participate in signal transduction pathways by interacting with activated receptors (28, 29). The distinct cytoplasmic region of Arcadlin suggests that it may be involved in different cell adhesion mechanisms and signal transduction pathways. Among other molecules induced in the hippocampus by seizures, Arc might be involved in the regulation of Arcadlin.

As Arc protein is induced in a similar time course to that of Arcadlin after seizures and is associated with F-actin (6), Arc-actin complex might regulate the adhesive activity and signal transduction by interacting with the cytoplasmic region of Arcadlin. Based on this hypothesis, we are currently examining whether Arc can associate with the cytoplasmic region of Arcadlin.

One important issue is whether or not Arcadlin functions as an adhesion molecule. Although protocadherin-1 and 2 show weak Ca\(^{2+}\)-dependent homophilic binding activity, protocadherin-3, the third protocadherin member, did not show significant cell adhesion activity (30, 31). We first performed a cell aggregation assay to show the homophilic binding activity such as that seen with classical cadherin family members. Like other protocadherins, stable arcadlin transfectants did not form large aggregates in the culture medium. We therefore carried out a cell adhesion assay (Fig. 5). Stable arcadlin transfectants bound to the extracellular domain of Arcadlin in a Ca\(^{2+}\)-dependent manner, but not to a control protein, BSA. Antibodies to Arcadlin completely blocked this binding. Thus, the in vitro homophilic interaction of Arcadlin appears to be weaker than that of classical cadherins; however, Bradley et al. (32) recently showed that Xenopus NP-protocadherin can mediate cell-cell adhesion as strongly as classical cadherins in vivo. Considering the unique structural features and cell adhesion properties of Arcadlin, the cell adhesion mechanisms may be different from those of classical cadherins. It is also possible that Arcadlin may interact with different types of cell adhesion molecules, or even the possibility of a ligand/receptor-type interaction.

We also investigated whether Arcadlin participates in synaptic transmission by treating hippocampal slices with Arcad-
lin antibodies. As they did not appear to affect LTP in the presence of Ca2+; we administered IgGs during a brief period of free Ca2+. Removal of Ca2+ results in a loss of cadherin-mediated adhesion (33) and a change in the structure of the cadherin extracellular domains from their native rodlike structure to a globular structure (34). After free Ca2+ treatment, Arcadlin antibody attenuated basal synaptic transmission and completely inhibited LTP induction. Suppression of basal transmission might reflect an anti-adhesive effect of the blocking antibody on synapses; however, the induction of arcadlin mRNA during LTP and the complete inhibition of LTP by the antibody strongly suggests specific involvement of Arcadlin in LTP induction. In contrast to our findings, the recent paper from Schuman's laboratory (27) showed the block of LTP by the N- or E-cadherin antibodies without affecting natural synaptic transmission. They found an inhibition of LTP in the presence of 1 mM Ca2+; however, the elevation of extracellular Ca2+ to 5 mM abolished this inhibition. The argument is made that the Ca2+ level at the synapse decreases during periods of high frequency stimulation and that this destabilizes “nascent” interactions. While this notion is applicable to the case of Arcadlin, there are little data to support it so far. In the future, the generation of knock-out mice will help to clarify the specific involvement of adhesion molecules in LTP.

Studies using antibodies or peptides that interfere with the binding of L1 and NCAM indicate that these molecules are also required for LTP induction (14, 15). Moreover, NCAM expression is known to be regulated by synaptic activity; however, changes typically occur over the course of days in contrast to the 2–4-h kinetics of Arcadlin (35). The mechanism to order these inductive events is not clear yet, except that the immediate early gene transcription factor Zif268 regulates the expression of synapsin I gene (36). While these transcription factors do not appear to bind to the promoter of NCAM gene, sequential induction of two kinds of adhesion molecules suggests that the rapid up-regulation of Arcadlin may selectively enhance synaptic contacts and provide a link between neural activity and subsequent actions of NCAM or constitutively expressed cadherins. Further studies of the molecular specificity of interaction, the subcellular targeting and possible signaling function of Arcadlin will be required to fully appreciate their role in the process of activity-dependent synaptic plasticity.

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