Specific phosphoproteins are targets of numerous extracellular signals received by astrocytes. One such target, which we previously described, is PEA-15, a protein kinase C substrate associated with microtubules. Two cDNAs differing in the length of their 3′-untranslated region (3′ UTR) were cloned from a mouse astrocytic library. Accordingly, Northern blots revealed two transcripts (1.7 and 2.5 kilobase pairs) abundant brain regions but also found in peripheral tissues. PEA-15-derived protein sequence (130 amino acids) shared no similarity with known proteins but is 96% identical to its human counterpart. In addition, several regions of the 3′ UTR share more than 90% identity between mouse and human. Different potential regulatory sequences are found in the 3′ UTR, which also completely includes the proto-oncogene MAT1. The high level of conservation of both the coding and the untranslated regions and the differential tissue distribution of the two transcripts of this major brain phosphoprotein suggest that not only the protein but also the 3′ UTR of PEA-15 mRNA play a role in astrocytic functions.

Astrocytes have to integrate many different extracellular signals with regard to their numerous functions (1, 2). For example, in the developing embryo, radial glia direct migrating neurons to their appropriate location and participate in determining their phenotype. Astrocytes also appear to be involved in the survival of mature neurons by releasing neurotrophic factors (3) and by providing neurons with nutrients (4). They also modulate neuronal transmission by removing ions and inactivating neurotransmitters. The presence on astrocytes of receptors for neurotransmitters, growth factors, hormones, and cytokines (5) allows extracellular signals to be transduced into intracellular cascades, such as the activation of specific protein kinases and phosphatases (6). Specific phosphoproteins are the targets of extracellular signals, and analysis of their function is likely to shed light on key regulatory steps involved in neuronal interactions.

Recently, we have described a novel protein kinase C substrate that is highly enriched in astrocytes, PEA-15 (7). This acidic 15-kDa phosphoprotein exists in vivo as three isoforms, namely N, Pa and Pb, which correspond to unphosphorylated, mono, and diphosphate forms, respectively. PEA-15 appears to be a protein required for mature astrocytic functions, because phosphorylation levels and phosphorylation increase during ontogenesis, maximal expression being reached in the adult brain (8). Moreover, PEA-15 phosphorylation is modulated by neurotransmitters or hormones, such as noradrenaline, vasoactive intestinal peptide, and endothelin. In addition to protein kinase C, calcium-calmodulin-dependent protein kinase II also phosphorylates PEA-15 (9). Thus, signals triggering increases in intracellular calcium concentrations result in an increased phosphorylation of PEA-15. The phosphorylation sites for both kinases were identified following protein purification, proteolytic cleavage, and microsequencing, and they were found to be different: LTRPSAKK for protein kinase C and DIIRQHPSEEEIK for calcium-calmodulin-dependent protein kinase II. Specific antibodies were raised against the two corresponding peptides that recognized PEA-15 in species ranging from fish to mammals (8), suggesting that an important regulatory feature of the protein is conserved. Finally, immunocytochemistry performed on intact astrocytes revealed that PEA-15 colocalizes with microtubules (8), whereas its level of phosphorylation changes either upon depolymerization or stabilization of tubulins, suggesting that PEA-15 could be involved in the morphological plasticity of astrocytes.

In the present study, we describe the isolation of PEA-15 cDNAs from an astrocytic cDNA library, their characterization, and their tissue distribution. Cloning and comparison with the human PEA-15 cDNAs reveals the conservation of both the coding and the noncoding regions of the transcripts, suggesting the presence of important regulatory sequences that are necessary both for the structure and function of these mRNAs and for their regulation.

**M. Kubes, A. Estellés, J. Glowinski, and H. Chneiweiss, manuscript in preparation.**

**M. Yokoyama and H. Chneiweiss, manuscript in preparation.**
Cloning of PEA-15 cDNAs from a Mouse Astrocytic Library—To increase the probability of cloning a full-length PEA-15 cDNA, a mouse astrocytic cDNA library was constructed (see "Materials and Methods"). A nucleotide probe was synthesized by PCR using degenerated primers whose sequences were deduced from the 19-amino acid peptide obtained after PEA-15 microsequencing. Using astrocytic cDNA as a template, the expected 57-bp PCR product was obtained, cloned, and sequenced, giving a unique central sequence of 27 bp.

The longest open reading frame (ORF) found in the 2.4-kb cDNA is 390 bp long with a 109-bp 5′ leader sequence and a 271-bp 3′ untranslated region. Comparison of the deduced amino acid sequence of the translated protein with the sequences obtained from two-dimensional SDS-polyacrylamide gel electrophoresis of mouse astrocyte proteins that could account for the thermostability of the protein suggested that the deduced protein sequence included the complete 1170-bp coding region. The 2.4-kb cDNA contains the same 390-bp ORF as the 2.4-kb cDNA. The ORF contains an in-frame termination codon, indicating that the methionine codon that initiated the 390-bp ORF is located within the nucleotide sequence GGCGTCATGG, which fulfills Kozak's criteria for a eukaryotic initiation codon (15).

Northern Blot Analysis—Total RNA from different tissues and cultured astrocytes (as described in Ref. 8) were extracted. RNA samples were electrophoresed through 1% agarose (Appligene) gels following standard procedures (13) and transferred to Hybond-N membranes (Amersham Corp.). A specific probe for the PEA-15 coding region was synthesized using PCR; the sense primer included the ATG initiation codon, whereas the antisense primer included the TGA termination codon. The expected 390-bp PCR product containing the complete mouse PEA-15 coding region was labeled using the RadPrime DNA labeling system (Life Technologies, Inc.) and [a-32P]dCTP. Two additional probes spanning different regions of the PEA-15 cDNA were obtained using PCR. The first, in the central region contained nucleotides 713-1754; the second, at the 3′ end included nucleotides 1755-2391. Specific binding was analyzed and quantified in a Packard InstantImager.

In Situ Hybridization—Brains were quickly removed from animals after decapitation and were kept frozen until sectioning. In situ hybridization was performed as described previously (14). [35S]Hiotemplate-labeled antisense and sense probes were made with T7 and T3 RNA polymerase (Stratagene), respectively, from a linearized plasmid containing the 2.4-kb PEA-15 cDNA. Sections were hybridized overnight at 50 °C with the antisense and sense probes in a buffer containing 40% formamide. After RNase treatment, the sections were dehydrated, delipidated, and air-dried. Standard autoradiography was carried out using NTB-3 emulsion (Kodak). Following development, slides were counterstained with hematoxylin and eosin.

**RESULTS**

The translated protein contains all of the four peptide sequences obtained by PEA-15 microsequencing including the phosphorylation sites for protein kinase C (Ser104) (7) and calcium-calmodulin-dependent protein kinase II (Ser116) (9). This probable initiation codon is preceded by an in-frame termination codon, indicating that some regulation of translation could occur at this level (16). In addition, in vitro translation, using rabbit reticulocyte lysates, resulted in the synthesis of a unique 15-kDa protein, recognized by an antibody raised against PEA-15, which is specific (Fig. 2).

The translated protein contains all of the four peptide sequences obtained by PEA-15 microsequencing including the phosphorylation sites for protein kinase C (Ser104) (7) and calcium-calmodulin-dependent protein kinase II (Ser116) (9). Thus, PEA-15 is a 130-amino acid protein with a predicted molecular mass of 15,054 daltons and a calculated isoelectric point of 5.12, in good agreement with previous results obtained from two-dimensional SDS-polyacrylamide gel electrophoresis migration of the endogenous protein (7).
**Fig. 1.** A, nucleotide and deduced amino acid sequence of the 2.4-kb PEA-15 cDNA isolated from mouse astrocytes. The ORF consists of 390 bp encoding for a 130-amino acid protein. Bold letters in the nucleotide sequence are the Kozak's consensus sequence, and putative polyadenylation signals in the 3'UTR are in bold and underlined letters. Underlined in the amino acid sequence are the consensus phosphorylation sites for protein kinase C and calcium-calmodulin-dependent protein kinase II, with an asterisk for the two serine phosphorylated by these two kinases. Also underlined are the two other peptides obtained after microsequencing. These sequences data are available from EMBL under accession numbers X86809 (HSPEA15) and X86694 (MMPEA15) for the human and mouse sequences, respectively. B, schematic alignments between mouse and...

Cloning of PEA-15 cDNAs
Fig. 2. Western blot analysis of in vitro translation products.
Translation products were electrophoresed in 15% polyacrylamide-SDS gels and blotted on polyvinylidene difluoride membranes. Left, translation products labeled with biotinylated lysine were detected by a chemiluminescent procedure (see "Materials and Methods"). Lanes 1 and 2, translation products of the PEA-15 sense RNA from two independent reactions. Lane 3, empty lane. Lane 4, translation products of the PEA-15 antisense RNA. Right panel, immunodetection of unlabeled translation products with the specific PEA-15 antibody revealed by chemiluminescent detection (see "Materials and Methods"); the two lanes contained translation products from two independent reactions.

proline described as essential for microtubule-binding of tau and MAP2 (18–20). In addition, a 20-amino acid-long stretch just upstream of the protein kinase C phosphorylation site is homologous to a conserved nonmotor domain found in microtubule-based molecular motors and dynein- and kinesin-related proteins, previously suggested to mediate protein-protein interactions and the formation of macromolecular complexes (21).

Tissue and Cellular Distribution of the PEA-15 Gene Expression—As previously indicated, cloning and sequencing of PEA-15 cDNA demonstrated the presence of two transcripts differing in the length of their 3'UTR. Accordingly, Northern blot analysis of total RNA from different tissues, using a labeled probe corresponding to the specific PEA-15 coding sequence, showed two transcripts of 2.5 and 1.7 kb (Fig. 3). These two mRNAs are abundant and have a widespread distribution in the central nervous system, particularly in the spinal cord, hypothalamus, and striatum (Fig. 3A). Indeed, the two transcripts are also found more ubiquitously at lower levels in several peripheral organs (Fig. 3B). The presence of detectable levels of PEA-15 mRNAs in peripheral tissues was surprising because Western blotting previously suggested that PEA-15 expression might be restricted to the central nervous system with the exception of eye and lung (Table I and Ref. 8). Interestingly, the relative amount of the 2.5- over the 1.7-kb transcript was very different according to the tissue or brain region considered, suggesting a regulation of the transcription termination and polyadenylation that could also influence translation efficiency (Table I).

Protein purification and microsequencing of the two phosphorylation sites within PEA-15 allowed the generation of highly specific polyclonal affinity purified antibodies (8). To determine which cells expressed PEA-15 in vivo, we compared PEA-15 immunoreactivity with that of well-established specific astrocytic marker glial fibrillary acidic protein. This was performed by double-labeling of coronal sections of the adult rat nervous system. Antibodies against PEA-15 mostly labeled astrocytes in all structures from the olfactory bulb to the spinal cord (Fig. 4, A and B). In addition, some neurons were also found to be PEA-15 positive (Fig. 4, C and D). By using the 2.4-kb cDNA, an RNA probe was synthesized for in situ hybridization on brain slices. A specific labeling was clearly observed, and the distribution of the PEA-15 mRNA corresponded to the protein localization as shown for example in the parietal and pyriform cortices (Fig. 5).

Comparison between Mouse and Human cDNAs—Nucleic acid data base searches found several human partial sequences (ESTs) highly similar to regions of the mouse PEA-15 cDNAs. The geneexpress program (Genethon, Evry, France) provided us with the clone c-ozl10, which we entirely sequenced, finding that it is the human counterpart of the mouse 1.6-kb DNA. Based on c-ozl10 sequence, it was possible to align multiple partially overlapping human ESTs. This allowed us to obtain a 2385-bp sequence that is the full-length human counterpart of the 2.4-kb PEA-15 mouse cDNA and then further confirmed after reverse transcriptase-PCR performed on human postmortem brain tissue and sequencing. Northern blots using human brain extracts confirmed the expression in vivo of these human PEA-15 cDNA sequences. Two cDNAs (2.4 and 1.6 kb) were found to code PEA-15 both in human and mouse. The percentages represent the homology between mouse and human cDNAs both in the coding and the noncoding regions. MAT1 is a reported transforming cDNA from a mouse mammary tumor cDNA library.
Interestingly, analysis of the sources of the libraries used to obtain 70 of these ESTs confirms the prominent expression of PEA-15 in the brain (44%), whereas significant expression also exists in many peripheral organs including placenta and liver (7% each), eye, lung, heart, endothelial cells, pancreas, testis and uterus (4% each), adrenal gland, prostate gland, kidney, and spleen (only one EST each).

Comparison of the mouse and human sequences revealed a striking degree of conservation. Like the mouse gene, two alternative polyadenylation signals were found in human sequences at bp 1536 for ATTAAA and bp 2261 for AATAAA, respectively. The PEA-15 coding sequence is 96% identical, coding for a highly conserved protein with 125 identical amino acids and only five conservative changes.

Human as well as mouse PEA-15 cDNAs have a long 3'UTR. Comparison of these 3'UTRs indicated three regions with identities greater than 90%, often over a stretch of more than 100 bp (e.g., in Fig. 1B, 390–570, 1410–1691, and 2180–2300 nucleotides). Several rare and potentially regulatory motifs are found in both species in these conserved regions. For example eight GGGNGGRR repeats in the 3'UTR of PEA-15 mRNA are also found in the glial-specific virus JCV (22).

Further analysis of the 2.4-kb PEA-15 cDNA 3'UTR revealed the sequence of the proto-oncogene MAT1. MAT1 is a nucleic acid sequence of 1.7 kb recently isolated from a chemically induced mouse mammary tumor on the basis of its transforming activity in NIH 3T3 cells (23). The entire MAT1 sequence is included within the 3'UTR of the 2.4-kb PEA-15 cDNA (nucleotides 713-2391). The occurrence of a chimeric clone is very unlikely because no restriction enzyme sites exist around the start site of this sequence. Furthermore, each of the 11 independently isolated mouse PEA-15 cDNA clones described here contained the MAT1 sequence, and more than 10 human ESTs encompass nucleotide 713 of PEA-15 cDNA and have additional upstream sequence; finally, we were able to directly
amplify the 2.4-kb PEA-15 cDNA from astrocytes by reverse transcriptase-PCR (data not shown), demonstrating that this sequence indeed exists in vivo.

To investigate the possible expression of a truncated PEA-15 mRNA that includes only the MAT1 region, additional Northern blot analyses were performed with several probes corresponding to three different regions of the 2.4-kb PEA-15 cDNA (Fig. 6). Probe A, designed as the PEA-15 coding region (bp 0–390) revealed two messages (1.7 and 2.5 kb), as did probe B, that corresponded to the 3′ UTR of the 1.6-kb PEA-15 cDNA (bp 613-1670, including the 5′ end of MAT1) (Fig. 6, A and B). By contrast, probe C, which includes the 3′ end of the 2.4-kb PEA-15 cDNA from bp 1670 to 2391 (which also includes the 3′ end of MAT1), only hybridized with the 2.5-kb mRNA (Fig. 6C). The same results were obtained with different normal peripheral tissues, including mammary glands and several tumors (data not shown). Furthermore, as shown on Fig. 2, it was never possible to observe a 6-kDa protein translated from the PEA-15 RNA, suggesting it is only able to express PEA-15 protein. Taken altogether, these findings demonstrate that the MAT1 proto-oncogene cDNA is a partial sequence of 1678 nucleotides of the 3′ UTR of PEA-15 not coding for another protein.

**DISCUSSION**

During the last two decades, numerous functions have been assigned to astrocytes, among which is their role as communicative cells (2). Intracellular phosphoproteins can be considered as targets for extracellular signals received by the cell (6). Their phosphorylation modifies their function and consequently some of the cell properties. However, very few specific astrocyte-enriched phosphoproteins are known, essentially the two main components of intermediate filaments: vimentin in immature cells and gial fibrillary acidic protein in mature astrocytes (24, 25). We have previously characterized PEA-15 as one of the major phosphoproteins in cultured astrocytes (7). Taking advantage of this enrichment, an astrocytic cDNA library was constructed to increase the relative abundance of PEA-15 transcripts in vivo. We demonstrated here that indeed PEA-15 is encoded by the longest ORF found in the isolated cDNAs because: (i) it contains all of the four peptide sequences previously established from protein microsequencing, (ii) it is translated in vitro as a 15-kDa protein, and (iii) it is expressed in vivo as demonstrated by Northern blotting and in situ hybridization.

The high expression of PEA-15 in astrocytes led us to focus on the function the protein could play in these cells in particular. However, a low but significant expression of the protein was also observed in neurons and oligodendrocytes grown in primary cultures (8). Data reported now support a more ubiquitous expression of the protein in vivo because immunohistochemistry performed on brain sections clearly revealed, beside astrocytes, subpopulations of PEA-15 positive neurons, and in situ hybridization confirmed these results at the mRNA level (Fig. 4 and 5). In addition, Northern blots indicate that expression of PEA-15 is predominant in the central nervous system; however, a significant but low level of PEA-15 transcripts is detected in several peripheral organs. This suggests additional functions for PEA-15 transcripts required in multiple cells and tissues, in addition to their specific role in astrocytes.

Phylogenetic conservation of the epitopes containing the two phosphorylation sites of PEA-15 was already suggested by Western blotting because specific antibodies allowed the detection of the protein in the brains of mammals, birds, and fish (8). Accordingly, the high homology (96%) between the human and mouse protein sequences established in the present study confirms this striking conservation and suggests a strong structural requirement for the function of the protein.

In addition to the remarkable conservation of the PEA-15 protein sequence, three highly conserved regions are found within the 3′ UTR of its cDNAs, each greater than 100 nucleotides in length. In mouse as well as in human, the two transcripts are presumably generated by the alternative use of the polyadenylation signals, which are found a dozen nucleotides upstream of the poly(A) tail of each cloned transcript. The 2.5-kb mRNA being always the most abundant form found in the central nervous system, diversity in the 3′ UTR of PEA-15 mRNA may result in differential stability or translation efficiency, as proposed for other eukaryotic mRNAs (for a review see Ref. 26).

3′ UTRs are also known to contain regulatory sequences that signal mRNA localization, translational regulation, and direct degradation (27–29). Conserved sequences found in mouse and human PEA-15 cDNA 3′ UTR are good candidates for such roles. Indeed, several infrequent regulatory motifs were found in these regions, including JCV repeats. The human J C polyomavirus (JCV) is the etiologic agent of the neurodegenerative disease progressive multiple leukoencephalopathy and replicates only in astrocytes. Several studies have established that the restricted host range of JCV to glial cells is determined at the level of viral transcription that is mediated by glial-enriched DNA-binding regulatory proteins (30, 31). Two 98-bp enhancer/promoter sequences have been characterized and recently demonstrated to bind two identified proteins: Pura and YB-1 (32). Thus, the PEA-15 gene might be one of the physiological targets of such trans-activators.

In addition, the 3′ UTR of the 2.4-kb PEA-15 cDNA contains the proto-oncogene MAT1. The MAT1 sequence was isolated from a mouse mammary tumor induced in vitro with N-methyl-N-nitrosourea and lithium and was reported to induce the oncogenic transformation of NIH-3T3 cells (23). A role for 3′ UTRs in transformation have been previously described. For example, α-tropomyosin 3′ UTR expression suppresses tumorigenicity (33, 34), whereas tropomyosin isoforms are frequently missing from spontaneously arising tumors (35), and in vitro transformation with oncogenes or viruses induces suppression of tropomyosin gene expression (36). Finally, expression of a cDNA encoding full-length tropomyosin suppresses transformation (37). PEA-15’s co-localization with microtubules and abundance in astrocytes could indicate that this protein plays a role in the regulation of morphological plasticity in astrocytes. Consequently, deregulation of its 3′ UTR (which contains the proto-oncogene MAT1) could contribute to tumorigenicity. In favor of this hypothesis, the expression of the protein was found...
to be lower in proliferating cells such as C6 glioma cell line (8).
Growing evidence shows that astrocytes are able to initiate dynamic responses when stimulated in vivo by a wide variety of extracellular signals. An important cellular response consists in increases in intracellular calcium that influence many astrocytic functions including cytoskeletal rearrangement and intercellular communication through calcium waves. As a major cytosolic phosphoprotein in astrocytes regulated by multiple calcium-dependent phosphorylation pathways, PEA-15 is ideally positioned to play a major role in signal integration. The present study also suggests a high degree of regulation at the level of translation, localization, and/or transcription of its mRNA and provides new tools to investigate PEA-15’s presumed role in and astrocytic growth and differentiation function both at the cellular and tissue level.

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