Rat synaptotagmin IV (SYT IV) is a depolarization-inducible synaptic vesicle protein. SYT IV homozygous mutant mice are viable and have deficits in fine motor coordination and some forms of memory. In this study, we report the identification of a human SYT IV orthologue. The predicted amino acid sequence of the human SYT IV clone is nearly 90% identical to the rat and mouse SYT IV proteins. In addition, human SYT IV has a characteristic serine for aspartate substitution within the first C2 domain that is conserved among Drosophila, Caenorhabditis elegans, mouse, and rat SYT IV sequences. The human SYT IV gene maps to chromosome band 18q12.3, a region that defines a break point in the synteny with mouse chromosome 18 and has been implicated by associated markers in two human psychiatric disorders. In the human neuroblastoma cell line SK-N-SH, SYT IV is an immediate-early gene inducible by elevated intracellular calcium and by forskolin, an activator of adenylyl cyclase. Expression of human SYT IV mRNA is restricted to brain and is not detectable in non-neuronal tissues. Within brain, human SYT IV mRNA is most highly expressed in hippocampus, with lower levels present in amygdala and thalamus. These results suggest a role for SYT IV in human brain function and in human neurological disease.

The synaptotagmins (Syts) are large family of proteins that function in vesicle trafficking. To date, 11 Syt isoforms have been identified (1–3). Syts are synaptic vesicle proteins (4–6) characterized by an intravesicular amino terminus, a short transmembrane domain, and a cytosolic region containing two structurally similar, but functionally distinct, regions homologous to the C2 domain originally described in protein kinase C (7). Through their C2 domains, Syts interact with a variety of presynaptic effector molecules including calcium and phospholipid (8), syntaxin (9), other Syts (10), AP-2 (11), and N- and P/Q-type Ca2+ channels (12).

Disruption of the murine syt I gene (13), or the Drosophila (14) and Caenorhabditis elegans (15) Syt genes, results in neonatal lethality or severe paralysis due to a dramatic impairment in evoked, calcium-dependent synaptic release. In addition, the C. elegans Syt mutants exhibit reduced retrieval of synaptic vesicles from the plasma membrane following depolarization (16). These observations suggest that Syts function both as calcium regulators in the exocytotic fusion reaction and as part of the endocytotic vesicle retrieval apparatus.

We identified a member of the Syt family, SYT IV, in a screen for neuron-specific immediate-early genes (IEGs) from the rat pheochromocytoma PC12 cell (17). Rat syt IV is an IEG in PC12 cells, inducible by depolarization with high potassium and by pharmacologic stimulation with forskolin (17). SYT IV mRNA is restricted to the rat neuroendocrine system, including brain and pituitary, and its levels are elevated in hippocampus and piriform cortex following kainic acid-induced seizures (17). In PC12 cells, following its stimulation-induced synthesis, SYT IV protein localizes to endoplasmic reticulum-Golgi complexes (18) and to secretory granules (6, 19). SYT IV protein can be found in endoplasmic reticulum-Golgi complexes and in axonal processes in cultured neurons (20). In contrast to SYT I null mice, which die shortly after birth (13), SYT IV homozygous mutant mice are viable and largely indistinguishable from wild-type littermates by appearance, home cage behavior, and basic neurologic function (21). However, consistent with its proposed role in modulation of synaptic function (22), SYT IV mutant mice have deficits in fine motor control and some forms of memory (21).

Unlike most other Syts, the rat SYT IV C2A domain has a single amino acid change that inactivates the calcium binding pocket and renders this domain incapable of binding calcium or phospholipid (23). This mutation, a serine for aspartic substitution at residue 244 (17), is also found in the murine (24), C. elegans, and Drosophila (22) SYT IV orthologues. We now report the identification of a human SYT IV orthologue that has strong homology with murine and rat SYT IV and contains the identical serine for aspartic acid substitution at residue 244, demonstrating this mutation is strongly conserved throughout evolution. Here, we map the chromosomal position of the human SYT IV gene to chromosome band 18q12.3. This chromosomal assignment suggests SYT IV may be a candidate gene in the psychiatric disorders schizophrenia and bipolar disease. In addition, the human SYT IV gene position defines
an evolutionary break point in regions of synteny between mouse and human chromosomes 18. The proximity of the SYT IV gene to this break point provides an opportunity to define the physical break point. Despite its location close to a break point, the human syt IV gene is transcriptionally regulated much like the rat SYT IV gene. Human SYT IV is inducible in the SK-N-SH human neuroblastoma cell line and is specifically expressed in brain but not in non-neuronal tissues.

EXPERIMENTAL PROCEDURES

Cell Culture—The SK-N-SH human neuroblastoma cell line (ATCC HTB-11) was propagated, as described by the supplier, in minimal essential medium, 0.1 mM non-essential amino acids, 1.0 mM sodium pyruvate, 10% fetal bovine serum at 37 °C in 5% CO2.

Human Synaptotagmin IV Sequence—The human expressed sequence tag data base available at the National Center for Biotechnology Information was used according to the BLAST algorithm. The human SYT IV cDNA sequence (residues 240–483) from the rat SYT IV sequence (17). From this search, a human clone (GenBank accession number A081755) with high homology to rat SYT IV was identified and obtained from Genome Systems (St. Louis, MO). This clone was sequenced and analyzed by partial restriction digest analysis. The human SYT IV nucleotide sequence discussed in this paper has been submitted to GenBank (accession number AF018242). The rat SYT IV nucleotide sequence is specifically expressed in brain but not in non-neuronal tissues.

RNA Analysis—SK-N-SH cells were grown to 70–80% confluence and shifted to serum-free conditions 18 h prior to stimulation. The cells were treated continuously with 50 μM forskolin, 50 ng/ml 12-O-tetradecanoylphorbol-13-acetate, or 10 μM calcium ionophore A23187 (Sigma) and 90 mM KCl were delivered for only 30 min and then removed, because the cells were rapidly killed during prolonged continuous treatments of these stimuli. At indicated times, total RNA was purified using the RNeasy Total RNA System (Qiagen, Santa Clarita, CA) according to the manufacturer’s instructions. 10 μg of total RNA from each time point was denatured for 10 min at 65 °C in 0.2 M SSC and 50% formamide and then washed an additional 3 times for 5 min at 55 °C in 0.1× SSC. Hybridized probe was detected using the cDNA probe was labeled with 35S-ATP using the terminal deoxynucleotidyl transferase method (25). Two FISH experiments were performed using the cDNA probe. The hybridization solution contained 400 ng of probe DNA, 3 μg of Cot 1 DNA, and 7 mg/ml salmon sperm DNA for 18 h at 42 °C. The filters were washed three times for 30 min at 65 °C in 0.2× SSC, 0.5% SDS. Rat-derived SYT I and GAPDH cDNAs were used as probes to map the gene to human chromosomes using fluorescence in situ hybridization (FISH) (25). Briefly, the cDNA probe was labeled with biotin-14-dATP (Life Technologies, Inc.) using nick translation and hybridized to metaphase chromosomes prepared from normal male peripheral blood lymphocytes using the bromodeoxyuridine synchronization method (25). Two FISH experiments were performed using the SYT IV probe. The hybridization solution contained 400 ng of probe DNA, 3 μg of Cot 1 DNA, and 7 μg of sonicated salmon sperm DNA per 10 μl of hybridization mixture (70% formamide, 10% dextran sulfate, and 2× SSC). This solution was denatured at 75 °C for 5 min, preannealed at 37 °C for 10 min, and applied to denatured chromosome slides. The slides were washed 4 times for 5 min at 44 °C in buffer containing 2× SSC and 50% formamide and then washed an additional 3 times for 5 min at 55 °C in 0.1× SSC. Hybridized probe was detected with avidin-conjugated fluorescein isothiocyanate (FITC, Vector Laboratories, Burlingame, CA). To increase the intensity of the FITC signals, two rounds of amplification were performed using biotinylated anti-avidin (Vector Laboratories). To generate clear reverse bands, metaphase chromosomes were counterstained with chromomycin A3 followed by distamycin A. The images were captured using the Photometric Chromosome Imaging System—a system created in the BDS image analysis system (ONCOR Imaging, Gaithersburg, MD).

RESULTS

Identification of a Human Synaptotagmin IV Orthologue—We sought to determine the following: 1) if a SYT IV orthologue exists in humans and 2) if this orthologue contains the conserved aspartate to serine substitution in the C2a domain. We searched the human expressed sequence tag (EST) data base for sequences homologous to the first 80 amino acids of rat synaptotagmin IV (17), a region of relatively little homology with other Syts. An EST with high homology (>90%) to the rat sequence was identified. This human EST is 4.5 kb in length and contains a polyadenylation signal at the 3′ end (data not shown). Sequencing of this clone confirmed high levels of homology with rat SYT IV cDNA throughout the entire open reading frame. The first 1671 nucleotides of the human clone are shown in Fig. 1. Overall, the predicted protein product of the human clone is 89.8% (372/425) identical to the rat SYT IV protein and 89.4% (370/425) identical to the murine SYT IV protein (Fig. 2A). For comparison, the rat and mouse sequences are 97.5% (414/425) identical.

Importantly, the human clone also contains, like the mouse, rat, and worm orthologues, a serine residue at position 244 within the first C2 (C2a) domain (Fig. 2A). In the rat protein, this amino acid residue replaces the conserved five aspartic acid residues shown to be critical for C2a domain structure (26), rendering rat SYT IV unable to bind calcium or phospholipid through its C2a domain (23). Rat SYT XI, which also contains this serine residue, has similar calcium binding properties (3).

Phylogenetic analysis of the human, rat, and mouse SYT IV proteins, and other Syts, clearly demonstrates that the human clone is a member of the SYT IV family (Fig. 2B). In
addition, as proposed previously (3), this analysis indicates a strong evolutionary link between SYT IV and SYT XI. Thus, because of the high level of overall identity and strong evolutionary relationship between the human clone and published SYT IV sequences from other species, and the presence of the conserved serine 244 residue, we refer to this EST clone as human SYT IV and presume it to be the human SYT IV orthologue.

The SYT IV Gene Maps to Human Chromosome Band 18q12.3—Our analysis of SYT IV function in mice indicates the SYT IV gene is not essential for survival (21). SYT IV homozygous mutant mice are generally indistinguishable from wild-type littermates by appearance and home cage behavior (21). SYT IV mutant mice do, however, exhibit deficits in motor performance and hippocampus-dependent memory (21). To determine if the SYT IV gene locus is associated with any known neurologic conditions in humans, we mapped the chromosomal position of the human SYT IV gene using FISH. A human SYT IV cDNA probe was used to map the gene to human chromosome band 18q12.3 (Fig. 3A). Over 60 cells were scanned on each slide, and a total of 55 metaphase images were captured and evaluated. FITC signals were clearly seen in the chromosome region of band 18q12.3 at its distal border with band 18q21 on two chromatids of at least one chromosome 18 in more than 50% of the cells counted (Fig. 3A). No other chromosomal sites with a pair of signals were detected in greater than one cell (1.0%). Two independent experiments were performed and both resulted in the same chromosomal assignment.

This assignment to band 18q12.3 distal defines the border between two adjacent regions of human chromosome 18 that are homologous to non-adjacent regions of mouse chromosome 18 (Fig. 3B). The more centromeric region of Mus musculus 18, defined by the gene for Mep1b, is homologous to Homo sapiens 18q11.2–12.3 (GDB:371066), whereas the neighboring telomeric mouse gene, catna1, maps to 5q21-22 (GDB:141920) (Fig. 3B). Therefore, the location of SYT IV in the telomeric sub-band region of H. sapiens 18q12.3 places the evolutionary break point between blocks of mouse and human homology at the border of H. sapiens 18q12.3-q21.1 and between the mouse homologues syt IV and catna1. This observation may facilitate the cloning of this break point in both mouse and human.

Interestingly, population studies suggest loci for bipolar dis-
order and schizophrenia susceptibility map within regions of chromosome 18 that include bands 18q12.1–12.3 (27). Both bipolar disease and schizophrenia have been attributed to abnormalities in neurotransmission (28, 29). Thus, the correct localization of the SYT IV gene to human chromosome 18q12.3 distal defines human and mouse evolutionary break points and may establish SYT IV as a candidate gene for the human psychiatric syndromes schizophrenia and/or bipolar disorder.

**Fig. 3.** Fluorescence in situ hybridization mapping of the human SYT IV gene to chromosome band 18q12.3 distal. A, a human chromosome preparation was hybridized with the biotinylated cDNA probe for the human SYT IV gene. The FITC signals were clearly seen on chromomycin A and distamycin A reverse-banded chromosome band 18q12.3 distal. Arrows indicate areas of FITC signal. B, an ideogram showing the map location of the human SYT IV gene on the region of human chromosome band 18q12.3 distal and its homologous region on *M. musculus* 18. The arrow on the left indicates the evolutionary break point on human chromosome 18. Shaded regions show the homologous regions between human and mouse.
Human SYT IV is Inducible in the SK-N-SH Neuroblastoma Cell Line—The SYT IV gene is transcriptionally up-regulated in response to variety of inducers in mouse and rat cell lines (17). In addition, rat SYT IV mRNA is specifically expressed in the brain and is not detectable outside the nervous system (17). Because the human SYT IV gene maps so closely to an evolutionary breakpoint in chromosome 18, we examined whether the human SYT IV gene was also inducible and had similar tissue specificity. By using the human neuroblastoma SK-N-SH cell line we find that, much like the rat and mouse genes, human SYT IV mRNA is rapidly and robustly induced by forskolin treatment. SYT IV mRNA levels peak at 4 h and decay to near base-line levels by 24 h (Fig. 4A). Human SYT IV mRNA is approximately 4.5 kb in size, running just below the 28 S ribosomal RNA band, indicating the EST clone is near full length. Agents that elevate intracellular calcium, e.g., the calcium ionophore A23187 (Fig. 4A) and potassium depolarization (data not shown), also lead to increases in the levels of SYT IV mRNA.

Induction of SYT IV expression by high potassium is not as robust as induction by forskolin in SK-N-SH cells. We have cloned several genes that are inducible in PC12 cells by forskolin and/or elevated potassium, and we examined their induction in rat brain following kainic acid-induced seizures (30–32). In nearly all cases, these genes, which are strongly induced by kainic acid in rat hippocampus, are more robustly induced by forskolin than by high potassium in PC12 cells. Interestingly, 12-O-tetradecanoylphorbol-13-acetate, a potent differentiation agent for the SK-N-SH cell line, does not substantially induce the SYT IV gene (data not shown). This result is similar to our observation in PC12 cells, where we find no SYT IV mRNA induction following treatment with the differentiation agent nerve growth factor (17).

To determine whether human SYT IV is an immediate early gene (IEG), inducible in the absence of protein synthesis through the activation of latent transcription factors, we analyzed the induction of SYT IV mRNA in the presence of a protein synthesis inhibitor, cycloheximide. Forskolin and high potassium depolarization induce SYT IV mRNA in SK-N-SH cells, even in the presence of cycloheximide, indicating human syt IV is an IEG (Fig. 4B).

Human SYT IV Expression Is Restricted to Brain—To investigate the tissue distribution of human SYT IV mRNA, we performed Northern blot analysis on purified poly(A)⁺ mRNA from various human tissues. SYT IV expression is restricted to brain and is not detectable in other tissues (Fig. 5). Rat SYT IV mRNA was similarly expressed only in brain and pituitary and was not detected in heart, muscle, lung, or liver (17). Like SYT IV, human SYT I is strictly expressed in brain (Fig. 5).

The distribution of SYT IV mRNA within human brain was also examined by Northern analysis. As observed in rat (17), human SYT IV is most highly expressed in hippocampus (Fig. 6). In addition, substantial levels of human SYT IV mRNA can be detected in amygdala and thalamus (Fig. 6). SYT I and SYT IV have similar distributions within brain, although quantitative differences are noticeable in the subthalamic nucleus and in caudate. Similar to their distribution in rat (17), both SYT I and SYT IV are generally expressed in a rostral to caudal gradient. Human SYT I and SYT IV are more highly expressed in thalamus than in caudate (Fig. 6). In rats, however, SYT I and SYT IV levels are equal in these regions (33), indicating subtle expression differences exist between rat and human.

**DISCUSSION**

SYT IV is a depolarization-inducible, labile protein with a metabolic half-life of approximately 2 h in the rat pheochromocytoma PC12 cell line (6). Following its stimulation-induced synthesis, SYT IV is rapidly transported to secretory granules (6, 19). In addition, SYT IV interacts with other components of
the presynaptic terminal, including syntaxin and SYT I (19), AP-2 (5), and N- and P/Q-type calcium channels (12).

Compared with SYT I-SYT I homo-oligomers, SYT IV-SYT I hetero-oligomers have a limited capacity to bind phospholipid (22), indicating that SYT IV can reduce the ability of SYT I to penetrate and bind phospholipid membranes, in effect functioning as a “dominant negative.” These data suggest SYT IV may modulate the calcium sensitivity of the vesicle fusion reaction in vivo. Thus, the relative levels of SYT IV protein in vesicles, modulated by neuronal stimulation, may alter the probability of vesicle fusion and lead to changes in synaptic output. Indeed, a 5-fold overexpression of SYT IV, relative to basal levels, in Drosophila neurons leads to a reduction in post-synaptic response at the fly neuromuscular junction (22). Because human SYT IV is an immediate early gene (Fig. 4B), it is rapidly induced by stimulation (Fig. 4A), and contains the inactivating serine for aspartate substitution (Fig. 2), the SYT IV protein may also function to attenuate synaptic responses at human synapses.

The assignment of the human SYT IV gene to chromosome 18 clearly differs from the heuristic assignment to chromosome 5 noted in GenBank™, an assignment that was predicted only by homology to the mouse genetic map. All genes currently mapping on human chromosome 18 are found on mouse chromosome 18, arranged in two blocks that are interrupted by a region homologous to human chromosome 5. Chromosomal band 18q12.3 and the SYT IV gene define an evolutionary break point between regions of mouse and human synteny (Fig. 3B), an observation that may facilitate the mapping of additional genes in the future. Moreover, this assignment is of interest with respect to evolution in that genes separated in the mouse by only 1.0 centimorgans (syt IV and catna1) are located on different human chromosomes. The precise localization of syt IV at the band 18q12 border supports the possibility that mammalian evolutionary break points tend to occur at discontinuities between functional and structural chromatin domains reflected in Giemsa (18q12) versus reverse bands (18q21) (34).

This fine definition provides the opportunity to determine the sequence of an evolutionary break point and may help to elucidate the mechanisms that predispose to evolutionary change across species. The mapping data presented here suggest that the SYT IV region of human chromosome 18, when compared with porcine, bovine, and murine chromosomes, is most similar to bovine chromosome 24. It has been suggested that the SYT IV region appears to have undergone a translocation involving chromosomes 1 and 6, whereas the murine chromosome contains an insertion (Fig. 3B). These events appear to have occurred independently but at a similar break point, an observation that may be confirmed by mapping of porcine and bovine syt IV genes.

It is worth noting that the region of human chromosome 18q12–22 has also been linked to schizophrenia and bipolar disease through chromosomal rearrangement mapping and population studies. In small family studies, chromosome 18 rearrangements, including a pericentric inversion of 18 (p1.31; q21.1) (35) and a translocation of 15;18 (pter-q13.3;q23-qter) (36), were found to segregate with schizophrenia. Similarly, epidemiological (37) and other population studies have suggested loci for bipolar disease and schizophrenia susceptibility exist in this region.

How might SYT IV play a role in schizophrenia and/or bipolar disease? The dysregulation of the dopaminergic system has an established role in human psychiatric disease (29). For example, abnormal increases in dopamine neurotransmission have been observed in the brains of schizophrenics (38) and are thought to contribute to the pathophysiological basis of this disease (39). SYT IV is expressed in dopaminergic brain regions (Fig. 6) and is present in secretory granules of rat PC12 cells (6), vesicles previously shown to contain dopamine (40). Thus, SYT IV may participate in the regulation of dopamine release in the human brain. A loss-of-function mutation or an alteration in levels of SYT IV may promote abnormal levels of dopamine release at dopaminergic synapses.

Our studies with SYT IV knockout mice have not specifically addressed the physiology of dopaminergic neurons but do support the suggestion that SYT IV modulates synaptic function (21). SYT IV homozygous mutant mice exhibit deficits in motor performance on the rotorod, a task sensitive to lesions of the basal ganglia that may alter normal dopamine levels (41). In addition, SYT IV mutant mice have deficits in hippocampus-dependent memory (21). Patients with schizophrenia also display memory deficits that have similarly been attributed to medial temporal lobe and hippocampal dysfunction (42, 43). The development of suitable animal models for schizophrenia has been problematic. However, such models often employ the use of psychostimulants such as cocaine (44). Interestingly, cocaine can induce SYT IV expression in rat striatum (45). Moreover, SYT IV has been suggested to play a role in the morphological changes brought about by exposure to psychostimulants (46).

In summary, we identified a human SYT IV orthologue highly homologous to rodent SYT IV proteins that contains a conserved amino acid substitution in its C2A domain. By using FISH, we mapped the human SYT IV gene to chromosome band 18q12.3. This chromosomal position defines an evolutionary break point between syntenic regions in mouse and human.
chromosomes 18. In addition, based on results of prior genetic linkage analysis, these data suggest SYT IV is a candidate gene for schizophrenia and/or bipolar disorder. Although near an evolutionary break point, human syt IV, like the rodent syt IV genes, is inducible in neuronal cell lines following stimulation and is specifically expressed in the brain but not in non-neuronal tissues.

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