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RAPID COMMUNICATION

Distinct Patterns of Gene Expression in the Left and Right Hippocampal Formation of Developing Rats

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ABSTRACT: A central problem in neurobiology is the elucidation of the mechanisms that underlie left–right asymmetries in brain structure and function. Using a transcriptome screening approach, we found asymmetric gene expression patterns in the right when compared with the left hippocampal formation at postnatal days (P) 6, 9, and 60 in the rat. Of those genes that were differentially expressed, most were predominantly expressed in the right hippocampus at P6, whereas most were predominantly expressed in the left at P9 and P60. Real-time PCR analysis of genes associated with synaptic vesicle trafficking confirmed this pattern. At P6, 9 of 13 such genes were more robustly expressed in the right hippocampus, while only 1 gene was predominantly expressed in the left. Conversely, at P9, 5 of the 13 genes were more highly expressed in the left hippocampus and only 1 gene was predominantly expressed in the right. This pattern persisted at P60: eight genes were more robustly expressed in the left hippocampus, and the remaining five showed no hemispheric preference. These data demonstrate a pattern of early lateralized gene expression that is likely to underlie the establishment of functional asymmetry in the adult hippocampus. © 2006 Wiley-Liss, Inc.

KEY WORDS: limbic system; lateralization; synaptic vesicle trafficking; synapse; transcriptome

INTRODUCTION

Since the discovery of the left hemispheric dominance of language abilities, cerebral lateralization of function has been well documented in humans (Geschwind and Levitsky, 1968). Left–right asymmetries are now known to be present in a variety of species, including rodents and nonhuman primates, suggesting an evolutionary origin for the lateralization found in humans (Bianki, 1981; Gannon et al., 1998). Numerous brain regions show left–right asymmetries, including the hippocampal formation, an area critical for certain forms of learning and memory in humans and rodents (Squire et al., 2004). In humans, the left hippocampus is associated with verbal memory (Tranel, 1991) and the right with spatial memory (Bohbot et al., 1998). Lateralization of the hippocampus may be a prerequisite for normal function in humans: left–right abnormalities in the hippocampus and associated limbic structures have been reported in autism and schizophrenia (Chiron et al., 1995; Schumann et al., 2004; Hanlon et al., 2005). In male rats, some portions of the right hippocampus are reportedly larger than the left (Diamond et al., 1983), whereas high affinity choline uptake is greater in the left than in the right (Kristofikova et al., 2004) and inactivation of the left, but not the right, impairs maze performance in aged animals (Poe et al., 2000). In adult male mice, Kawakami et al. (2003) demonstrated that the ϵ2 subunits of the *N*-methyl-D-aspartate (NMDA) receptor are distributed asymmetrically on hippocampal CA1 pyramidal neurons.

Although it is reasonable to assume that developmentally regulated, differential gene expression provides the foundation for lateralized brain functions, only a few studies have addressed this possibility. Sun et al. (2005) showed asymmetric gene expression in embryonic human right and left cerebral cortex, suggesting that the molecular basis of lateralization may be established early in humans. Left–right asymmetries have not been examined in developing rodents, but studies show that gene expression patterns change dramatically during the first few postnatal weeks (Mody et al., 2001; Stead et al., 2006).

The goal of the present study was to examine the molecular basis of hippocampal lateralization during early postnatal development in the rat by evaluating gene expression patterns in right and left hippocampi at postnatal days (P) 6, 9, and 60. We used transcriptome profiling (Kroes et al., 2006) to analyze the expression of distinct families of genes and qRT-PCR to determine the expression of genes associated with synaptic vesicle trafficking at each age in each hippocampus.

Female Sprague-Dawley rats with litters and young adult male rats were obtained from Charles River Labs

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TABLE 1.

Hemispheric Differences in Genes Expressed in the P6 Rat Neonatal Hippocampus (at <1% FDR)

Accession no.	Fold change[a]	Gene ID	Function
Synapse function			
K03486	1.553	Protein kinase C type III	Intracellular signaling cascade
D90035	1.393	Calcineurin A-α	Calcium-dependent protein phosphatase activity
D84450	1.383	Na^+, K^+-ATPase, β3 subunit	Ion transport
S59158	1.372	Glutamate transporter	Neurotransmitter transport
J04625	1.365	Carboxypeptidase H	Peptide hormone processing
U03390	1.260	Protein kinase C receptor	Signal transduction
M91590	1.194	β-Arrestin2	G-protein coupled receptor protein signaling
S62933	1.179	Receptor tyrosine kinase, TrkC(ki14)	Signal transduction
M23601	1.174	Monoamine oxidase B, Maobf3	Neurotransmitter degradation
AF089730	1.141	Potassium channel subunit (Slack)	Ion transport
D30781	1.132	Phospholipase A2 receptor	Intracellular signaling
U88324	1.072	G protein, β1 subunit, rGb1	G-protein coupled receptor signaling pathway
Synaptic vesicle trafficking			
AF044581	1.196	Syntaxin 13	Vesicle-mediated transport
U63740	1.209	Synaptotagmin binding zygin I (fez1)	Vesicle translocation and docking
Glycolysis			
X02231	1.359	Glyceraldehyde-3-phosphate-dehydrogenase	Glycolysis
X07467	1.230	Glucose-6-phosphate dehydrogenase	Glucose metabolism
D28561	1.130	Glucose transporter, GLUT4	Carbohydrate transport
Microtubules			
U30938	1.470	Microtubule-associated protein 2, MAP2	Microtubule assembly
V01227	1.393	α-Tubulin	Microtubule-based process
Synaptogenesis			
L21192	1.449	GAP-43	Synaptogenesis/growth
Other			
X62952	1.648	Vimentin	Structural molecule activity
E12625	1.302	Novel protein that is expressed with nerve injury	Unknown
AF306546	1.187	Blood-brain barrier specific anion transporter, BSAT1	Ion transport
M91652	1.226	Glutamine synthetase, glnA	Nitrogen fixation
D38492	1.220	Neural adhesion molecule F3	Cell adhesion
U77777	1.209	γ-Interferon inducing factor, α-isoform	Immune response
S45392	1.201	Heat shock protein 90	Protein folding
M17523	1.128	Peptide tyrosine-tyrosine (YY)	Regulation of GI motility
U50194	1.119	Tripeptidylpeptidase II	Proteolysis/peptidolysis
AB018546	1.112	SERP1	Protein amino acid glycosylation

Positive values are indicative of an increase in gene expression in right relative to left, whereas negative values are indicative of a decrease.
[a]The fold change was calculated between mean values of the P6 right ($n = 6$) and P6 left ($n = 6$) hippocampi.

(Wilmington, MA). Six male rats were selected from three litters at P6 and six from the same three litters at P9; animals were anesthetized and decapitated. Six male young adults were anesthetized and decapitated at P60. Brains were removed and placed in ice-cold artificial cerebral spinal fluid, and the hemispheres were separated. Each hippocampus was removed and weighed. There were no differences in the average weights of left and right hippocampi at each age (data not shown). The hippocampi were stored in RNA*later* (Ambion, Austin, TX) at $-8^{\circ}C$ until assayed. All procedures were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Animal Care and Use Committees of the University of Texas at San Antonio and Evanston Hospital.

The rat CNS microarray platform used in these studies has been described in detail elsewhere (Kroes et al., 2006). Briefly, the 1,178 genes represented on the microarrays were strategically chosen to represent the majority of characterized ontological categories within the rat genome. The individual sequences of the gene-specific oligonucleotides were stringently determined to eliminate cross-reactivity and to provide uniform hybridization efficiency. The dynamic range, discrimination power, accuracy, reproducibility, and specificity of the resultant microarrays allowed for the detection of significant expression

TABLE 2.

Hemispheric Differences in Genes Expressed in the P9 Rat Neonatal Hippocampus (at <1% FDR)

Accession no.	Fold change[a]	Gene ID	Function
Synapse function			
S60953	1.249	Receptor tyrosine kinase (TrkC(ki39))	Signal transduction
M17069	−1.739	Calmodulin, RCM3	G-protein coupled receptor protein signaling
X55812	−1.583	CB1 cannabinoid receptor, SKR6	G-protein coupled receptor protein signaling
D00698	−1.299	Insulin-like growth factor I	Signal transduction
L14323	−1.282	Phospholipase C-β1b	Intracellular signaling
M15880	−1.219	Neuropeptide Y	Neuropeptide signaling pathway
M23601	−1.148	Monoamine oxidase B, Maobf3	Neurotransmitter degradation
Glycolysis			
X02231	−1.303	Glyceraldehyde-3-phosphate-dehydrogenase	Glycolysis
J04218	−1.681	Glucokinase	Glucose homeostasis
M68971	−1.599	Hexokinase type II	Glycolysis
U73859	−1.552	Hexokinase type III	Glycolysis
NM_012734	−1.407	Hexokinase 1	Glycolysis
Microtubules			
AF459021	−1.651	Neuron-specific class III β-tubulin	Microtubule-based movement
U72353	−1.617	Lamin B1	Intermediate filament
AB011679	−1.591	Class I β-tubulin	Microtubule-based movement
AB015946	−1.549	Tubulin	Microtubule-based movement
X66870	−1.448	Lamin A	Intermediate filament
V01217	−1.317	β-Actin	Cell motility
V01227	−1.294	α-Tubulin	Microtubule-based movement
Other			
X62085	−1.844	Hypoxanthine-guanine phosphoribosyltransferase	Nucleoside metabolism
X06827	−1.746	Porphobilinogen deaminase	Heme biosynthesis
S73424	−1.734	Migration inhibitory factor	Inflammatory response
E12625	−1.201	Novel protein that is expressed with nerve injury	Unknown

Positive values are indicative of an increase in gene expression in right relative to left, whereas negative values are indicative of a decrease.
[a]The fold change was calculated between mean values of the P9 right ($n = 6$) and P9 left ($n = 6$) hippocampi.

changes as small as 10%. Importantly, although smaller changes may actually demonstrate statistical significance, a 10–13% change, in our hands, is currently the limit of discrimination for qRT-PCR quantitation.

Total RNA was extracted from the right and left hippocampi with guanidine isothiocyanate and CsCl-ultracentrifugation, purified (Qiagen, Valencia, CA), and used as the substrate for RNA amplification and labeling using optimized procedures based on the Eberwine protocol (Van Gelder et al., 1990). For all analyses, a reference experimental design was used and utilized a universal rat reference RNA (Stratagene, La Jolla, CA) treated concurrently with the samples. Cohybridization, washing, and subsequent scanning parameters were stringently controlled, resulting in high-quality measurement of fluorescent intensities that were used for statistical quantitation. Prior to normalization of the fluorescent signals, several quality confidence measurements were calculated for each scanned array to assess overall quality and to ensure that acceptable tolerance limits were not exceeded. Results from LOWESS-normalization of the signal intensity data were then analyzed using the permutation-based SAM-RS (Significance Analysis of Microarrays using Rank Scores; Van de Wiel, 2004) at a stringent false discovery rate (FDR) of <5% and subsequently coupled with GOMiner-based ontological analyses (Zeeberg et al., 2003). Sequentially combining these two algorithms added statistical rigor to the analyses of coregulation of multiple genes (gene sets) and is capable of demonstrating significant correlations between the expression of specific gene sets and complex phenotypic distinctions even if individual genes do not.

All primer sets, individual primer concentrations, and final amplification conditions were optimized prior to analysis. Dissociation curves were performed on all reactions to assure product purity. Original input RNA amounts were calculated by comparison to standard curves using purified PCR product as a template for the mRNAs of interest and were normalized to amount of β2 microglobulin (B2M). Experiments were performed in triplicate for each data point.

Results of the microarray analyses indicated statistically significant differences in the expression of a number of genes between left and right hippocampi at all three ages (Tables 1–3). Stringent statistical analyses (by SAM-RS) at <1% FDR identified 30, 23, and 27 genes at P6, P9, and P60, respectively,

TABLE 3.

Hemispheric Differences in Genes Expressed in the P60 Rat Hippocampus (at <1% FDR)

Accession no.	Fold change[a]	Gene ID	Function
Synapse function			
L27487	1.166	Calcitonin receptor-like receptor, CRLR	G-protein coupled receptor protein signaling
U12336	−1.140	Acetylcholine receptor α9 subunit (nAChR)	Cholinergic synaptic transmission
M64236	−1.119	Substance P receptor, SPR	Neuropeptide signaling pathway
J04625	−1.105	Carboxypeptidase E, CPE	Peptide hormone processing
S42358	−1.100	GABA transporter	Neurotransmitter transport
X95579	−1.097	GABA rho-1 subunit	Neurotransmitter receptor activity
NM_012944	−1.096	Dopamine receptor D4, Drd4	G-protein coupled receptor protein signaling
AF005720	−1.082	Chloride channel, ClC-2	Chloride transport
D90035	−1.259	Calcineurin A-α	Calcium-dependent protein phosphatase activity
Synaptic vesicle trafficking			
AF007758	−1.490	Synuclein 1 mRNA	Synaptic vesicle biogenesis and organization
Glycolysis			
X02231	−1.167	Glyceraldehyde-3-phosphate-dehydrogenase	Glycolysis
M27466	−1.043	Cytochrome oxidase subunit VIc, COX-VIc	Electron transport
Microtubules			
X66870	−1.408	Lamin A	Intermediate filament
AB015946	−1.305	Tubulin	Microtubule-based movement
U72353	−1.144	Lamin B1	Intermediate filament
Other			
E13644	1.206	Neurodap-1	Protein sorting
K01701	1.138	Oxytocin/neurophysin, Oxt	Neurohypophyseal hormone activity
M86742	1.090	Neurotrophin-4, NT-4	Growth factor activity
M19533	−1.259	Cyclophilin	Protein folding
X06827	−1.231	Porphobilinogen deaminase	Heme biosynthesis
X54793	−1.228	Heat shock protein, hsp60	Protein folding
U23055	−1.188	C-CAM4 gene	Cell–cell adhesion
M86389	−1.182	Heat shock protein, hsp27	Protein folding
X62085	−1.164	Hypoxanthine-guanine phosphoribosyltransferase	Nucleoside metabolism
NM_013180	−1.131	β4 integrin, Itgb4	Cell–matrix adhesion
X73683	−1.143	Histone H3.3	DNA binding/brain development
M63122	−1.079	Tumor necrosis factor receptor	Tumor necrosis factor receptor activity

Positive values are indicative of an increase in gene expression in right relative to left, whereas negative values are indicative of a decrease.
[a]The fold change was calculated between mean values of the P60 right ($n = 6$) and P60 left ($n = 6$) hippocampi.

which were differentially expressed. At P6, all of these genes were more highly expressed in the right hippocampus, whereas at P9, almost all were more highly expressed in the left hippocampus. Only one gene was more highly expressed in the right at P9. At P60, almost all differentially expressed genes were preferentially expressed in the left hippocampus. GOMiner analysis, used to identify functional gene families (Kroes et al., 2006), showed that most of these genes appeared to fall into at least five developmentally relevant, major ontological categories (Tables 1–3).

Because a large percentage of the differentially expressed genes at each age were associated with synaptic function, we used qRT-PCR to examine the expression patterns of 13 additional genes primarily associated with synaptic vesicle trafficking. Specifically, we chose genes encoding proteins that function at the active zone of the synapse (Sudhof, 2004). Table 4 shows that the majority of these genes were predominantly expressed in the right hippocampus when compared with the left at P6, mimicking the overall expression patterns observed in the microarray dataset. At P9, 5 of 13 were more highly expressed in the left and 7 were equally expressed in the two hippocampi; only 1 gene, Rab 15, showed a higher expression in the right hemisphere. On P60, 8 of the 13 genes were expressed more robustly in the left hippocampus and the remainder showed no hemispheric preference.

This is the first report of a left–right asymmetrical pattern of differential gene expression in a cortical structure during development. Results showed that differential gene expression is lateralized by P6 in the rat hippocampal formation and begins to switch from right to left dominance by P9. Previous studies indicated that many genes are highly expressed in the rodent hippocampus during the first two postnatal weeks, including those related to synapse formation and function (Mody et al., 2001; Stead et al., 2006). Although functional asymmetries

TABLE 4.

qRT-PCR Analysis of Synaptic Vesicle Trafficking Genes

Gene ID	P6 (R vs. L)	P9 (R vs. L)	P60 (R vs. L)
Synuclein 1	n/s	n/s	pL = 0.022
Syntaxin 13	pR = 0.050	pL = 0.042	n/s
Fez1	pR = 0.008	n/s	n/s
Rab 15	pR < 0.001	pR < 0.001	pL < 0.001
Rab 3a	pL = 0.011	n/s	pL = 0.021
Rab 3b	pR = 0.010	n/s	pL < 0.001
Rab 3c	pR = 0.032	pL = 0.025	n/s
Vamp 2	n/s	n/s	pL = 0.022
Vamp 3	n/s	pL < 0.001	pL = 0.026
Munc 13	pR < 0.001	pL < 0.001	pL < 0.001
Sv2b	pR < 0.001	n/s	n/s
RIMS	pR = 0.021	n/s	n/s
Pclo	pR = 0.028	pL = 0.053	pL = 0.001

For each gene, transcript abundance, normalized to β2-microglobulin, was quantified by Brilliant SYBR Green qRT-PCR using optimized primer sets. Data from six independent samples per group were compared. Values are expressed as *P*-values (paired Student's *t* test). The directionality of gene expression is denoted. n/s, not significant; pL, predominant expression in the left hippocampus; pR, predominant expression in the right hippocampus.

have not been examined in neonates, a number of critical developmental events occur in the rat hippocampal formation at the end of the first week. For example, there is a dramatic increase in dendritic spines after P7, and synaptic plasticities such as long-term potentiation (LTP) are first elicited at about this same time (Zimmer, 1978; Teyler et al., 1989; Jones et al., 2003; O'Boyle et al., 2004). Our finding of a right-to-left shift in the expression of synaptic vesicle trafficking genes between P6 and P9 suggests that synaptic function may be lateralized early in the period of functional development. Future morphological and physiological studies comparing right and left hippocampi in neonates will be of considerable interest.

The early lateralization of gene expression seen here is in agreement with a recent report from Sun et al. (2005) showing asymmetry of gene transcription in the embryonic human cortex. They found lateralized gene expression in the frontal, perisylvian, and occipital regions at 12 and 14 weeks, a period of neuronal proliferation and migration. Here we found lateralized expression at P6 in the rat; the peak of granule cell proliferation in the dentate gyrus occurs at about P7, and there is extensive growth and development of synaptic connections throughout the hippocampal formation at this time. Interestingly, our results showed that GAP-43 (Benowitz and Routtenberg, 1997) was more highly expressed in the right hippocampus than the left at P6, suggesting that temporal and/or spatial patterns of axonal growth and synaptogenesis may be lateralized in neonatal rodents.

In humans, the right cortex appears to develop before the left (Geschwind and Galaburda, 1985), and several studies suggest that visuospatial and language abilities are initially localized to the right hemisphere in infants and then become localized to the left in adults (Chiron et al., 1997). Our data suggest that a similar right-to-left shift may occur during hippocampal development and maturation. Furthermore, the identification of this shift may be relevant to studies of schizophrenia and autism, diseases that have been linked to developmental abnormalities in the hippocampal formation and associated structures (Schumann et al., 2004; Hanlon et al., 2005). Interestingly, Hemby et al. (2002), using a microarray approach, demonstrated marked differences in gene expression in schizophrenic brains when compared with controls, including a robust down-regulation of mRNAs associated with synaptic vesicle proteins in the hippocampal formation in the schizophrenic brains. Perhaps a significant component regulating the emergence of the schizophrenic phenotype is a perturbation in the normal asymmetric gene expression patterns that occur early in development.

The lateralized gene expression pattern found here in young adult rats supports the idea that there are morphological and/or physiological differences in the two hippocampi. Although very few investigators have considered such differences, several reports indicate that they occur. For example, Kawakami et al. (2003) found that the ϵ2 subunit of the NMDA receptor is asymmetrically distributed between left and right hippocampi in young adult mice. Furthermore, using in vitro recordings, they demonstrated that an ϵ2 subunit antagonist reduced commisure LTP in CA3 pyramidal neurons located in the left hippocampus but not in those in the right hippocampus. Additionally, there are reports of lateralized differences in hippocampal volume in rats (e.g., Diamond et al., 1983). Whether these differences are reflected in some aspect of behavioral lateralization is not clear. Although previous studies have failed to identify behavioral differences following lesions of either the right or the left hippocampus using standard assays in young adult rodents, lateralized function has been documented in aged rats. When Poe et al. (2000) inactivated one hippocampus or the other in young adult rats, they saw no effect on spatial maze learning. In aged rats, however, they found performance decrements with inactivation of the left hippocampus but not the right. They suggested that these could result from dysfunction of the aged right hippocampus or greater involvement of the left hippocampus in spatial learning.

Data presented here demonstrate a unique asymmetrical pattern of differential gene expression in the rat hippocampal formation between P6 and P60. While future in situ hybridization and immunocytochemical studies will be necessary to localize these expression patterns to subregions of the hippocampal formation, our finding that representative genes from a number of ontological categories were differentially expressed in the same asymmetric pattern suggests that lateralization may be a global feature of this region during both early development and young adulthood.

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