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Differential alterations of kainate receptor subunits in inhibitory interneurons in the anterior cingulate cortex in schizophrenia and bipolar disorder

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Abstract

The aim of this study was to examine whether glutamatergic inputs onto GABA interneurons via the kainate receptor in the anterior cingulate cortex may be altered in schizophrenia and bipolar disorder. Hence, in a cohort of 60 post-mortem human brains from schizophrenia, bipolar disorder, and normal control subjects, we simultaneously labeled the mRNA for the GluR5 or GluR6 subunit of the kainate receptor with [^{35}S] and the mRNA for the 67 kD isoform of the GABA synthesizing enzyme glutamic acid decarboxylase $(GAD)_{67}$ with digoxigenin using an immunoperoxidase method. The density of the GAD_{67} mRNA-containing neurons that co-expressed GluR5 mRNA was decreased by 43% and 40% in layer 2 of the anterior cingulate cortex in schizophrenia and bipolar disorder, respectively. In contrast, the density of the GAD_{67} mRNA-containing cells that expressed GluR6 mRNA was unaltered in either condition. Furthermore, the amount of GluR5 or GluR6 mRNA in the GAD_{67} mRNA-expressing cells that contained a detectable level of these transcripts was also unchanged. Finally, the density of cells that did not contain GAD_{67} mRNA, which presumably included all pyramidal neurons, but expressed the mRNA for the GluR5 or GluR6 subunit was not altered. Thus, glutamatergic modulation of inhibitory interneurons, but not pyramidal neurons, via kainate receptors containing the GluR5 subunit appears to be selectively altered in the anterior cingulate cortex in schizophrenia and bipolar disorder.

Keywords: Glutamate; GABA; Gene expression; In situ hybridization; Post-mortem human brain

1. Introduction

The anterior cingulate cortex (ACCx) specializes in the monitoring, processing, and integration of cognitive and emotive information (Allman et al., 2001; Barbas, 2000; Carter et al., 1998; Devinsky et al., 1995; Paus, 2001) and has long been strongly implicated in the pathophysiology of a variety of neuropsychiatric diseases, among them schizophrenia and bipolar disorder (Benes, 2000; Carter et al., 2001; Chana et al., 2003; Eastwood and Harrison, 2001). Although the precise nature of alteration of neural circuits within the ACCx in these disorders remain to be

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Table 1
Cases used in the present study

Case	Age	PMI	Sex	Hemisphere	Race	CE	pH	Psychotropics received at time of death	Cause of death
Bipolar disorder									
1	83	17.5	M	R	W	0 (>12)	6.60	Divalproex	Cardiopulmonary failure
2	74	22.9	F	R	W	100	U	Divalproex, lorazepam, olanzapine	Cardiopulmonary failure
3*	26	22.8	F	L	W	0 (>62)	6.35	Lithium, lorazepam	Cardiopulmonary failure
4	52	17.2	F	R	W	200	U	Olanzapine	Hepatic failure
5	62	13.4	F	R	W	0 (>12.2)	U	Divalproex, buproprion, sertraline	Breast cancer
6	74	7.2	M	L	W	100	6.70	Gabapentin, olanzapine	Pneumonia
7	85	27.5	F	L	W	534	6.28	Olanzapine, divalproex	Cardiopulmonary failure
8*	51	31	M	L	W	0 (>23)	7.02	Clonazepam, gabapentin	Suicide by overdose
9	69	29.5	M	L	W	0 (>48)	U	Lithium	Pneumonia
10*	64	11	F	R	W	800	6.26	Trifluoperazine	Respiratory failure
11*	42	15.8	F	L	W	960	6.60	Lithium, divalproex, perphenazine	Medication overdose, rule out suicide
12	29	10.7	F	L	W	200	6.70	Divalproex, lithium, clonazepam, olanzapine	Cardiac arrest
13	36	9	M	L	W	U	U	Unknown	Suicide
14*	73	20.8	F	R	W	50	6.32	Carbamazepine, risperidone	Sepsis
15*	74	14.3	M	R	W	400	6.27	Divalproex, lithium, olanzapine, hydroxyzine prn, lorazepam prn, zolpidem prn	Pneumonia
16*	62	18.7	F	R	W	100	6.40	Divalproex, sertraline, risperidone, benztropine, donepezil	Renal failure
17	82	5.0	M	L	W	U	6.37	Unknown	Cardiopulmonary failure
18	40	30.8	M	R	W	200	6.60	Gabapentin, ziprasidone, citalopram, risperidone, topiramate	Cardiac arrest
19	38	22	M	R	W	200	6.24	Divalproex, paroxetine, olanzapine	Carbon monoxide poisoning
20	47	16.3	F	R	W	50	U	Divalproex, topamirate, tiagabine, perphenazine, klonazepam,	Cardiopulmonary arrest
Mean	58.1± 18.7	18.2± 7.7	M:F=10:10	R:L=11:9		212.3± 282.8	6.48± 0.23		
Schizophrenia									
21	85	15.7	F	R	W	150	U	Risperidone, lorazepam	Sepsis
22	48	33.8	F	L	W	450	6.63	Risperidone, divalproex	Cardiac failure
23*	44	19	M	L	W	266	6.20	Clozapine	Pneumonia
24*	89	13.5	F	L	W	20	U	Trifluoperazine	Pneumonia
25	78	13.4	F	L	W	750	6.81	Haloperidol, lithium, cogentin	Sinus node disease
26	61	19.9	M	R	W	300	6.68	Clozapine	Sepsis
27	61	11	F	R	W	150	U	Paroxetine, clonazepam, clozapine	Myocardiac infarction
28*	84	25.8	F	R	W	0 (71.6)	6.14	None	Cardiac arrest
29*	26	16	M	R	W	357	6.75	Fluphenazine decanoate	Suicide by hanging

(continued on next page)