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Deficits in $GABA_B$ receptor system in schizophrenia and mood disorders: a postmortem study

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Abstract

Postmortem and genetic studies have clearly demonstrated changes in $GABA_B$ receptors in neuropsychiatric disorders such as autism, bipolar disorder, major depression, and schizophrenia. Moreover, a number of recent studies have stressed the importance of cerebellar dysfunction in these same disorders. In the current study, we examined protein levels of the two $GABA_B$ receptor subunits GABBR1 and GABBR2 in lateral cerebella from a well-characterized cohort of subjects with schizophrenia (n=15), bipolar disorder (n=14), major depression (n=13) and healthy controls (n=12). We found significant reductions in protein for both GABBR1 and GABBR2 in lateral cerebella from subjects with schizophrenia, bipolar disorder and major depression when compared with controls. These results provide further evidence of GABAergic dysfunction in these three disorders as well as identify potential targets for therapeutic intervention.

Keywords

$GABA_B$ receptor; schizophrenia; bipolar disorder; major depression; lateral cerebellum

1. Introduction

Gamma-aminobutyric acid (GABA) acts as the main inhibitory neurotransmitter in the central nervous system. There are three GABA receptor types, $GABA_A$, $GABA_B$, $GABA_C$. Both $GABA_A$ and $GABA_C$ are ligand-gated Cl^- channels that mediate the fast-inhibitory action of GABA (Olsen and Homanics, 2000). In contrast, the $GABA_B$ receptor is metabotropic, associated with K^+/Ca^{2+} channels, is G-protein linked, and produces slow inhibitory signals (Bowrey, 2000). $GABA_B$ receptors are heterodimeric and consist of two

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subunits: GABA B receptor 1 (GABBR1) and GABA B receptor 2 (GABBR2). The GABBR1 gene produces two splice variants, GABBR1A and GABBR1B (Kaupmann et al., 1997). Functional $GABA_B$ receptors require both the GABBR1 and GABBR2 subunits. The $GABA_B$ receptor is known to modulate release of a number of neurotransmitters including dopamine, serotonin, noradrenaline, somatostatin, glutamate and GABA (Nyitrai et al., 2003; Sakamaki et al., 2003; Steiniger and Kretschmer, 2003; Takahashi et al., 2010; Waldmeier et al., 2008).

Because of its roles, $GABA_B$ receptors have been examined for their impact on psychiatric disorders. A series of studies have shown $GABA_B$ abnormalities in disorders including autism (Fatemi et al., 2009; Oblak et al., 2010), bipolar disorder (Ishikawa et al., 2005), major depression (Ghose et al., 2011; Klempan et al., 2009; Sequiera et al., 2009) and schizophrenia (Ishikawa et al., 2005; Mizukami et al., 2000, 2002; Zai et al., 2005). Our laboratory observed significant reductions in GABBR1 protein in cerebellum, superior frontal cortex, and parietal cortex of subjects with autism and a significant reduction in GABBR2 in cerebellum of subjects with autism (Fatemi et al., 2009). Oblak et al. (2010) found significantly reduced $GABA_B$ receptor density in the anterior and posterior cingulate cortex and the fusiform gyrus of subjects with autism. Reductions in GABBR1A, GABBR1B, and GABBR2 proteins were also observed in prefrontal cortex of subjects with bipolar disorder (Ishikawa et al., 2005). A series of immunohistochemical experiments similarly found reductions in $GABA_B$ immunolabeling in hippocampus, prefrontal cortex, inferior temporal cortex, and the entorhinal cortex of subjects with schizophrenia (Ishikawa et al., 2005; Mizukami et al., 2000, 2002). The loci of both the GABBR1 gene (6p21.3) and GABBR2 gene (5q34) have been established as susceptibility loci for schizophrenia (Lindholm et al., 1999; Petryshen et al., 2005). However, one study has found a weak linkage between the GABBR1 gene and schizophrenia (Zai et al., 2005), while two other studies have found no connection (Imai et al., 2002; Zhao et al., 2007). In two microarray studies of suicides, increased expression of GABBR1 and GABBR2 mRNA was observed (Klempan et al., 2009; Sequiera et al., 2009). A further study found increased mRNA for GABBR2 in dentate gyrus of subjects with depression while there was decreased mRNA expression for GABBR1A in the same region (Ghose et al., 2011).

Schizophrenia affects approximately 1% of the population (Mueser and McGurk, 2004), generally manifests itself during adolescence and early adulthood and is characterized by the presence of symptoms including hallucinations, and delusions (APA, 1994). Bipolar disorder is characterized by alternating episodes of mania and depression or mania alone (Bipolar I) or episodes of depression and hypomania (Bipolar II) (APA, 1994). Major depressive disorder is characterized by the presence of one or more episodes consisting of five or more symptoms including depressed mood, changes in sleep and appetite, loss of energy, anhedonia, indecisiveness, feelings of worthlessness, and suicidal ideation that occur during the same two week period and represent a change from previous functioning (APA, 1994).

In the current study we have examined protein levels of GABBR1 and GABBR2 in cerebellum, a brain region that has been implicated in the pathology of schizophrenia, bipolar disorder, and major depression (Andreasen et al., 1996; Baldaçara et al., 2008; Konarski et al., 2005; Krüger et al., 2003; Liotti et al., 2002; Loeber et al., 2002; Smith et al., 2002) and because of a lack of information regarding $GABA_B$ receptors in this region, particularly with regard to subjects with bipolar disorder and major depression. We used lateral cerebellar tissue from a well-characterized cohort of subjects with schizophrenia, bipolar disorder, major depression, and controls from the Stanley Medical Research Institute. We hypothesized that, similar to what has been found in other brain regions, that

both GABBR1 and GABBR2 protein would be reduced in all three diagnostic groups when compared with controls.

2. Experimental/Materials and Methods

2.1. Brain Procurement

The current study has been approved by the Institutional Review Board of the University of Minnesota-School of Medicine. Postmortem lateral cerebella were obtained from the Stanley Foundation Neuropathology Consortium under approved ethical guidelines. The collection consisted of 15 subjects with schizophrenia, 14 subjects with bipolar disorder, 13 with major depression without psychotic features and 12 normal controls. All groups were matched for age, sex, race, postmortem interval and hemispheric side (Table 1). All demographic information and medical data including lifetime use of psychotropic medications and history of drug abuse were provided to us by the Stanley Foundation consortium (Table 1).

2.2. SDS-PAGE and Western Blotting

Western blotting experiments for GABBR1 and GABBR2 were performed as previously described (Fatemi et al., 2009). Each gel contained samples from subjects with schizophrenia, bipolar disorder, major depression, and controls in order to minimize interblot variability. The primary antibodies used were anti-GABBR1 (NB300-160, Novus Biologicals (Littleton, CO) 1:1,000), anti-GABBR2 (56311, QED Bioscience Inc. (San Diego, CA) 1:1,000), anti-neuronal specific enolase (ab16808, (Cambridge, MA), 1:2,000), and anti-β actin (A5441, Sigma Aldrich (St. Louis, MO), 1:5,000). Secondary antibodies used were goat anti-rabbit IgG (A9169, Sigma Aldrich, (St. Louis, MO), 1:80,000) and rabbit anti-mouse IgG (A9044, Sigma Aldrich, (St. Louis, MO) 1:80,000). The molecular weights of approximately 108 kDa (GABBR1), 105 kDa (GABBR2), 46 kDa (NSE), and 42 kDa (β-actin) immunoreactive bands were quantified with background subtraction. Results obtained are based on at least two independent experiments.

2.3. Statistical Analysis

All protein measurements for each group were normalized against both NSE (Table 2) and β-actin (Table 3) and expressed as ratios of GABBR1/NSE, GABBR1/β-actin, GABBR2/NSE, and GABBR2/β-actin. Statistical analysis was performed as previously described (Fatemi et al., 2008, 2010a,b) with $p<0.05$ considered significant. Briefly, group comparisons were conducted using analysis of variance (ANOVA). If the group differences were significant, follow-up independent t-tests were conducted. Group differences on possible confounding factors were explored using chi-square tests for categorical variables and ANOVA for continuous variables. Where group differences were found, analysis of covariance was used to explore these effects on group differences for continuous variables and factorial ANOVA with interaction terms for categorical variables. All analyses were conducted using SPSS v.17 (SPSS Inc, Chicago, IL).

3. Results

All protein measurements for GABBR1 and GABBR2 were normalized against two housekeeping proteins: neuronal specific enolase (NSE) and β-actin. Analyses of Variance identified group differences on GABBR1/β-Actin ($F(3,48)=7.64$, $p<.001$), GABBR1/NSE ($F(3,48)=11.03$, $p<.001$), GABBR2/β-Actin ($F(3,48)=10.95$, $p<.001$), and GABBR2/NSE ($F(3,48)=9.90$, $p<.001$). Individual t-tests were performed comparing control subjects vs. those with bipolar disorder, major depression, and schizophrenia. We observed a significant reduction in GABBR1 in subjects with bipolar disorder ($p<0.006$, GABBR1/NSE; $p<0.012$, GABBR1/β-actin), major depression ($p<0.0023$, GABBR1/NSE; $p<0.023$, GABBR1/β-

actin), and schizophrenia ($p<0.0001$, GABBR1/NSE; $p<0.0007$, GABBR1/β-actin) when compared with controls (Figures 1 and 2; Tables 2 and 3). GABBR2 was also reduced in subjects with bipolar disorder ($p<0.010$, GABBR1/NSE; $p<0.0063$, GABBR1/β-actin), major depression ($p<0.0025$, GABBR1/NSE; $p<0.0020$, GABBR1/β-actin), and schizophrenia ($p<0.0003$, GABBR1/NSE; $p<0.0001$, GABBR1/β-actin) when compared with controls (Figures 1 and 2, Tables 2 and 3). There were no significant differences in protein levels of NSE and β-actin between controls and subjects with bipolar disorder, schizophrenia, or major depression (Figure 1, Tables 2 and 3), indicating that the decreased expression of GABBR1 and GABBR2 in cerebellum were not the result of differences in neuronal cell numbers between the four groups.

No significant differences were found between groups on hemisphere side, ethnicity, gender, history of substance abuse or severity of substance abuse, post mortem interval (PMI), age, brain pH, or brain weight (Table 1). While PMI did not reach significance, the longer average PMIs for schizophrenia, bipolar disorder, and major depression when compared with controls could influence results adversely. We also compared the three diagnostic groups on family history, suicide, fluphenazine equivalents, and duration of disease and found no significant differences (Table 1). Age of onset was significantly later (32.7 years) for depressed compared to schizophrenics (23.2) and bipolar subjects (21.6), ($F(2,39)=4.5$, $p=.017$). Analyses of variance (ANOVAs), controlling for age of onset, found no effect on the protein levels of GABBR1 or GABBR2. Finally, we did find significant differences on tissue freezer time between controls (1072 days), depressed (1136 days), bipolar (1335 days) and schizophrenics (1351 days), ($F(3,50)=4.93$, $p=.004$). However, when ANOVAs were run with freezer time as a covariate, there was no impact on our results, indicating that freezer time had no impact on the observed reductions in GABBR1 and GABBR2 protein levels in the diagnostic groups.

4. Discussion

In the current study we found that there were significant reductions in GABBR1 and GABBR2 in lateral cerebellum of subjects with schizophrenia, bipolar disorder, and major depression. These results were specific for GABBR1 and GABBR2 as there were no changes in housekeeping genes β-actin or NSE. Analysis of confounds found no effect of any confound on protein data.

Consistent with our finding of reduced GABBR1 in cerebella, GABBR1 been shown to be reduced in other brain regions of subjects with schizophrenia (Ishikawa et al., 2005; Mizukami et al., 2000, 2002). Immunohistochemical studies have shown the reduction in GABBR1 immunoreactivity were specific to granular cells in the hippocampus (Mizukami et al., 2000) and pyramidal cells in the hippocampus, inferior temporal cortex, prefrontal cortex (PFC), and entorhinal cortex while there was no such reduction in interneurons (Ishikawa et al., 2005; Mizukami et al., 2000, 2002). Ishikawa et al., (2005) found no such reduction in GABBR2 immunoreactivity or protein levels in PFC of subjects with schizophrenia. The difference between GABBR1 and GABBR2 expression in this region may suggest differential expression of these subunits in PFC. Our finding of reduced GABBR2 protein in cerebella may point to regional differences in GABBR2 expression. Mizukami et al., (2002) suggested that the reduction of GABBR1 in pyramidal cells, and consequent reduction of $GABA_B$ receptors, could result in dysfunction of inhibitory mechanisms in these cells and increased signal output.

GABAergic dysfunction and consequent dysfunction of inhibitory mechanisms may underlie two of the most common forms of information processing deficits in schizophrenia, prepulse inhibition (PPI) and P50 suppression. DBA/2J mice, an animal model for schizophrenia,

which display disrupted PPI also display decreased $GABA_B$ expression in both prefrontal cortex and hippocampus when compared with C57BL/6J controls (Bortolato et al., 2007). Moreover, the $GABA_B$ receptor agonist baclofen has been shown to correct PPI deficits in DBA/2J mice and in rats (Bortolato et al., 2004, 2007). Baclofen has been tested as a potential therapy for schizophrenia, but while an initial study showed that adjunctive baclofen treatment resulted in improvement of symptoms (Frederiksen, 1976), a subsequent study showed no efficacy (Bigelow et al., 1977). P50 suppression has been demonstrated to involve alpha-7 nicotinic receptor-mediated release of GABA (for a review, see Martin et al., 2004). The atypical antipsychotic drug clozapine significantly improves P50 gating in subjects with schizophrenia (Adler et al., 2004) and it has been suggested that clozapine's efficacy may occur through the potentiation of $GABA_B$-mediated inhibition (Daskalakis and George, 2009).

Compared with schizophrenia, there is less evidence of a link between $GABA_B$ receptors and bipolar disorder. Studies have found no differences in levels of GABA in brain of subjects with bipolar disorder, when compared with controls (Kaufman et al., 2009). Moreover, while recent research has demonstrated influence of $GABA_A$ receptors in bipolar disorder (Craddock et al., 2010), there have not been any studies implicating GABBR1 or GABBR2 in bipolar disorder. However, glutamic acid decarboxylase 65 kDa and 67 kDa proteins (GAD 65/67) are downregulated in cerebella of subjects with bipolar disorder, schizophrenia, and major depression (Fatemi et al., 2005) providing evidence of GABAergic dysfunction. Additionally there are reductions in GABBR1A, GABBR1B, and GABBR2 in prefrontal cortex of subjects with bipolar disorder as measured by western blotting (Ishikawa et al., 2005). Our finding of reduced GABBR1 and GABBR2 protein in cerebella of subjects with bipolar disorder provides further evidence of GABAergic dysfunction in bipolar disorder and supports previous findings by Ishikawa et al (2005) in the same disorder.

Altered expression of mRNA for GABBR1 and GABBR2 has been found in brains of subjects with major depression and victims of suicide (Klempan et al., 2009; Sequeira et al., 2009; Ghose et al., 2011) implicating $GABA_B$ receptor dysfunction in these disorders. A recent paper found that there was a reduction in mRNA for GABBR1A and an increase in GABBR2 mRNA in dentate gyrus while there were no changes in mRNA for GABBR1A, GABBR1B, or GABBR2 in cerebellum, cingulate cortex, or orbitofrontal cortex in subjects with major depression (Ghose et al., 2011). The discrepancy between this finding and our observation of reduced protein in cerebella of subjects with major depression may be due to several reasons including discordance between mRNA and protein levels, splicing events, and receptor downregulation in response to negative feedback loop causing increased mRNA as well as differences of measuring mRNA vs. protein. We have previously shown differences in mRNA and protein levels for GABBR1 in subjects with autism (Fatemi et al., 2009, 2010c). We found that while there was a concordant downregulation of mRNA and protein for GABBR1 in cerebellum, in parietal cortex there was a significant increase in mRNA despite significant reduction in protein levels (Fatemi et al., 2009, unpublished observations). Altered expression of $GABA_B$ receptor genes has been found in brain regions of suicide victims (Klempan et al., 2009; Sequeira et al., 2009). Importantly, Sequiera et al (2009) found that GABBR2 was upregulated in suicides who also had major depression when compared with non-depressed suicides.

Chronic administration of antidepressants has been shown to increase expression of $GABA_B$ receptors in brain of animal models of major depression (Nakagawa and Ishima, 2003; Pratt and Bowery, 1993). However, statistical analysis of our data showed lack of antidepressant effect on $GABA_B$ receptor levels in cerebellum of subjects with schizophrenia, bipolar disorder, or major depression (data not shown). $GABA_B$ receptor antagonists have been

found to produce antidepressant properties in animal models, as have GABBR1 deletion studies (Nakagawa et al., 1999; Heese et al., 2000; Mombereau et al., 2005). Moreover, a study found that treatment of subjects with major depression with baclofen resulted in a worsening of symptoms (Post et al., 1991). These findings have led some to believe that an overactive GABA system contributes to major depression (Ghose et al., 2011). Further experiments are needed to determine the role of anti-depressants on $GABA_B$ receptor function.

Reports of cerebellar involvement in higher brain functions beyond motor control, such as cognition and emotion, go back several decades (reviewed by Konarski et al., 2005; Baldaçara et al., 2008). Patients with cerebellar degeneration were shown to display dementia and psychosis (Schut, 1950) and patients with cerebellar lesions have been shown to display a flattening of emotion, disinhibition of restraint, and passivity, conditions similar to what has been observed in manic and depressed states or in schizophrenia (Schmahmann and Sherman, 1998). Circuits connecting the cerebellum with regions of the prefrontal cortex associated with executive function, verbal memory and language have been identified (Schmahmann and Pandya, 1995) and disruption of prefrontal-thalamic-cerebellar circuitry has been hypothesized to result in cognitive deficits associated with schizophrenia (Andreasen et al., 1996). Reduction of cerebellar volumes have been reported in subjects with schizophrenia, bipolar disorder, and major depression (reviewed by Konarski et al., 2005; Baldaçara et al., 2008). Reduced cerebellar activation has been observed in functional imaging studies of subjects with schizophrenia (Crespo-Facorro et al., 2001, 2007), bipolar disorder (Loeber et al., 2002; Krüger et al., 2003) and major depressive disorder (Liotti et al., 2002; Smith et al., 2002). Particularly relevant to the current study, reduced activation of lateral cerebellum was observed in patients with schizophrenia on tasks that involved memory (Crespo-Facorro et al., 2001).

Our findings of reduced expression of GABBR1 and GABBR2 in lateral cerebellum provide further evidence of GABAergic dysfunction in schizophrenia, major depression, and bipolar disorder. Future studies need to examine additional brain regions such as hippocampus and prefrontal cortex. Additionally, $GABA_A$ receptors should be examined in the same brain regions to obtain a more complete picture of GABAergic dysfunction in schizophrenia and mood disorders.

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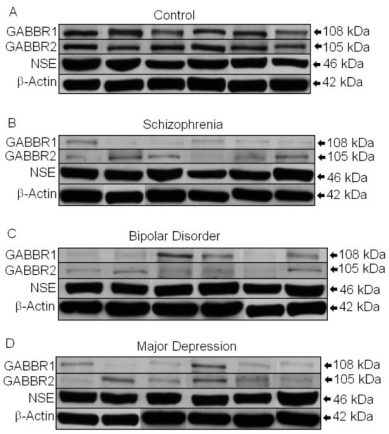

Figure 1.

GABBR1 and GABBR2 are reduced in lateral cerebella of subjects with schizophrenia (B), bipolar disorder (C), and major depression (D) when compared with healthy controls (A). NSE and β-actin are unchanged when compared across groups (A–D).

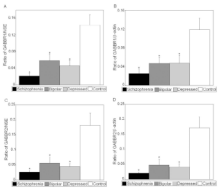

Figure 2.
Mean GABBR1/NSE (A), GABBR1/β-actin (B), GABBR2/NSE (C), and GABBR2/β-actin (D) ratios for control, bipolar, depressed, and schizophrenic subjects are shown for cerebellum. (Error bars expressed as standard error of the mean.) *, $p<0.05$.

Table 1

Demographic information for the four diagnostic groups

	Bipolar	Depression	Control	Schizophrenia	F or χ^2	p
Age	43.6 (11.1)	45.5 (8.35)	47.7 (8.6)	44.5 (13.1)	0.35	0.79
Sex	5F, 9M	5F, 8M	4F, 8M	6F, 9M	0.149	0.99
Race	13W, 1B	13W	11W, 1B	12W, 3A	13.2	0.15
PMI	33.1 (16.6)	28.3 (11.3)	22.8 (9.08)	33.7 (14.6)	1.85	0.15
pH	6.16 (0.234)	6.17 (0.235)	6.25 (0.261)	6.16 (0.256)	0.39	0.76
Side of Brain	7R, 7L	4R, 9L	7R, 5L	6R, 9L	2.22	0.529
Brain Wt	1434 (176)	1479 (145)	1501 (169)	1472 (108)	0.45	0.72
Family hx	0.859 (0.77)	0.692 (0.48)	0	1.13 (0.834)	2.91	0.066
Suicidal death	8 (5 violent)	7 (2 violent)	0	4 (2 violent)	3.44	0.49
Drug/Alc hx	0.786 (0.802)	0.462 (0.66)	0.25 (0.622)	0.533 (0.743)	1.25	0.30
Freezer storage time (days)	1335 (168)	1136 (300)	1072 (204)	1351 (233)	4.93	**0.004**
Age of onset	21.6 (8.63)	32.7 (13.9)	--	23.2 (7.96)	4.51	**0.017**
Duration	21.1 (9.17)	12.8 (11.4)	--	21.7 (11.2)	2.96	0.064
Severity of Substance abuse	1.86 (2.03)	1.25 (2.09)	0.167 (0.577)	1.2 (1.86)	1.25	0.303
Severity of Alcohol abuse	2.07 (1.9)	1.92 (2.14)	1.17 (1.03)	1.47 (1.6)	0.74	0.532
Fluphenazine (lifetime)	21,780 (24,630)	--	--	52,270 (62,060)	2.94	0.098

Schizophr Res. Author manuscript; available in PMC 2012 May 1.

Table 2

Western blotting results for GABBR1, GABBR2, and NSE in lateral cerebellum of subjects with schizophrenia, bipolar disorder, major depression vs. matched controls

Group	GABBR1/ NSE	Δ	P	GABBR2/NSE	Δ	P	NSE	P
Control	0.144 ± 0.087	RG	RG	0.182 ± 0.141	RG	RG	20.2 ± 3.34	RG
Bipolar	0.059 ± 0.056	↓59%	**0.006**	0.056 ± 0.076	↓69%	**0.010**	20.2 ± 3.24	NS
Depression	0.046 ± 0.046	↓68%	**0.0023**	0.045 ± 0.036	↓75%	**0.0025**	21.6 ± 2.87	NS
Schizophrenia	0.022 ± 0.022	↓85%	**0.0001**	0.026 ± 0.022	↓86%	**0.0003**	20.1 ± 1.67	NS

RG, reference group; NS, not significant

Table 3

Western blotting results for GABBR1, GABBR2, and β-actin in lateral cerebellum of subjects with schizophrenia, bipolar disorder, major depression vs. matched controls

Group	GABBR1/β-Actin	Δ	P	GABBR2/β-Actin	Δ	P	β-Actin	P
Control	0.119 ± 0.084	RG	RG	0.172 ± 0.129	RG	RG	24.9 ± 3.57	RG
Bipolar	0.046 ± 0.048	↓61%	**0.012**	0.048 ± 0.070	↓72%	**0.0063**	26.5 ± 3.11	NS
Depression	0.047 ± 0.058	↓61%	**0.023**	0.042 ± 0.036	↓76%	**0.0020**	25.3 ± 5.25	NS
Schizophrenia	0.025 ± 0.036	↓79%	**0.0007**	0.021 ± 0.016	↓88%	**0.0001**	25.2 ± 4.21	NS

RG, reference group; NS, not significant