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Regional differences in expression of β-tubulin isoforms in schizophrenia

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ABSTRACT

A growing body of evidence suggests that abnormal elements of the cytoskeleton may be associated with the pathophysiology of schizophrenia. Isoforms of a major cytoskeleton protein, β-tubulin, were recently demonstrated to have distinct roles in neuronal differentiation and cell viability. For these reasons, we tested the hypothesis that there are differences in the expression of β-tubulin isoforms (βI-βIV) in the brain in schizophrenia, using western blot analysis in an elderly group of subjects with this illness and a control group. We found that βI-tubulin protein expression was decreased in the anterior cingulate cortex and increased in the dorsolateral prefrontal cortex, but not changed in superior temporal gyrus or hippocampus in schizophrenia. Our data supports the growing body of evidence suggesting abnormalities of the cytoskeleton in schizophrenia.

1. Introduction

The cytoskeleton, a dynamic composition of structural proteins, contributes to the function and morphology of dendrites, spines, synapses, and a myriad of biological processes including cell division and chemotaxis. Preclinical studies have demonstrated that elements of the cytoskeleton contribute to neuroplasticity via the dynamic process of spine and synapse formation, including changes in cytoskeletal and scaffolding proteins (Prabakaran et al., 2004; Beasley et al., 2006; Clark et al., 2006; Behan et al., 2009; English et al., 2009; Martins-de-Souza et al., 2010). Converging experimental evidence implicates abnormalities of the cytoskeleton in the pathophysiology of schizophrenia (Prabakaran et al., 2004; Behan et al., 2009; English et al., 2009; Martins-de-Souza et al., 2010).

One cytoskeletal protein, β-tubulin, is a major component of axons, dendrites, and dendritic spines. β-tubulin has multiple isoforms including βI, βII, βIII, and βIV. Each β-tubulin isoform may have specific functions. A recent knockdown study of tubulin isoforms found unique roles for each of the isoforms in neuronal differentiation (Guo et al., 2010). For example, knockdown of βI, but not βII, decreased viability of neuroblastoma cells in culture, while knockdown of βII decreased neurite density. Knockdown of βIII decreased cell viability when cells were treated with exogenous glutamate and glycine, suggesting a role for this isoform in protection against free radicals and reactive oxygen species (Guo et al., 2010). Finally, βI may directly inhibit actin tubule formation, decreasing cellular adhesion and spreading (Lezama et al., 2001). While the specific functional roles of the tubulin isoforms remain to be fully elucidated, these data suggest that the tubulin isoforms may have unique functional roles.

Studies of β-tubulin protein expression in schizophrenia, using antibodies that detect all of the isoforms of β-tubulin, have not found changes in β-tubulin expression (Clinton et al., 2006; Bauer et al., 2009). The conventional view of β-tubulin as a housekeeping gene, reinforced by the absence of changes in pan-β-tubulin protein expression in postmortem studies, has led to the widespread use of β-tubulin as a loading control for western blot analyses (Clinton et al., 2006; Bauer et al., 2009; Ghose et al., 2009). Nevertheless, growing evidence for cytoskeletal disturbances in schizophrenia and the notion that specific isoforms of β-tubulin have unique roles in cellular function suggest that there may be isoform-specific abnormalities of β-tubulin expression in schizophrenia. Thus, we tested the hypothesis that there are differences in expression of β-tubulin isoforms in the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), hippocampus (HC) and superior temporal gyrus (STG) in subjects with schizophrenia and a comparison group.

2. Materials and methods

2.1. Subjects and tissue preparation

Postmortem brain samples were obtained from Mount Sinai Medical Center brain collection. These subjects were recruited prospectively and

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underwent a thorough antemortem diagnostic and clinical assessment (Table 1). Subjects were excluded for a history of alcoholism, death by suicide, or coma for more than 6 h before death occurred. Consent was also obtained from each subject's next of kin. Brains were collected at autopsy and sliced into 1 cm thick coronal slabs. The dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), hippocampus (HC), and the superior temporal gyrus (STG) were dissected from the slabs using anatomical landmarks, frozen with dry ice, and stored at −80 °C until used. Gray matter was dissected from tissue slabs and was pulverized, adding liquid nitrogen as necessary, then stored at −80 °C. Pulverized tissue for western blot analysis was reconstituted in 5 mM Tris HCl, 0.32 M sucrose, to which a Complete Mini protease inhibitor tablet (Roche Diagnostics, Manheim, Germany) was added. Tissue was then homogenized with a Power Gen 125 homogenizer (Thermo Fischer Scientific, Rockford, IL) on speed 5 for 60 s. Homogenates were assayed for protein concentration using a BCA protein assay kit (Thermo Fischer Scientific, Rockford, IL). Homogenates were stored at −80 °C until used for western blot analysis.

2.2. Western blot analysis

Previously characterized antisera specific to the βI, βII, βIII, and βIV isoforms were used for this study (Banerjee et al., 1988, 1990, 1992). The antisera were empirically tested to determine antisera dilutions as well as cross reactivity with the human isoforms of β-tubulin. βI, βII, and βIII antisera were used at a 1:1000 dilution and βIV was used at a 1:500 dilution. Valosin containing protein (VCP) was used as a loading control at a 1:5000 dilution. VCP was chosen as a loading control because VCP was previously determined to be unchanged in schizophrenia patients compared to control subjects (Stan et al., 2006; Bauer et al., 2009). Samples were loaded randomly (by diagnosis) for all studies. Samples for western blot analysis were placed in reducing buffer with β-mercaptoethanol and heated to 70 °C for 10 min. 15 μg of protein was loaded in each lane and run in duplicate by SDS-PAGE on 4 to 12% polyacrylamide gels (Invitrogen, Carlsbad, California) at 180 V for 1 h. For all of our western blot assays, 15 μg of loaded protein was within the linear range of detection. Gels were transferred to polyvinylidene fluoride membrane on a semi-dry transblotter (Bio-Rad, Hercules, California) at 18 V for 40 min. The membranes were then bathed in blocking buffer (LiCor, Lincoln, Nebraska) for 1 h at room temperature. Subsequently, membranes were probed with primary antibodies in blocking buffer. Primary antibody incubations were performed at 4 °C overnight. Membranes were next washed 3 times for 5 min each in 0.01% Tween phosphate buffered saline. Membranes were probed with near IR-dye labeled secondary antibodies (LiCor, Lincoln, Nebraska) at a 1:5000 dilution in blocking buffer for 2 h in the dark at room temperature. Membranes were then washed three times for 5 min each in 0.01% Tween phosphate buffered saline, and then briefly washed in water three times. Blots were imaged with the LiCor Odyssey laser based imaging system (Bond et al., 2008).

2.3. Data analysis

Using the Odyssey 3.0 analytical software, near infrared fluorescent signals obtained from the LiCor Odyssey scanner were expressed as raw integrated intensity with top–bottom median intra-lane background subtraction (Bond et al., 2008). Samples were run in duplicate. Each replicate was first normalized to VCP expression from the same lane of the same blot, and then the ratio of tubulin/VCP was averaged for each subject yielding one normalized value per subject for each protein analyzed. Data were analyzed using Statistica (Statsoft, Tulsa, Oklahoma). Correlation analyses were performed to probe for associations between the expression of the isoforms of β-tubulin and tissue pH, age, and postmortem interval. One way analysis of variance (ANOVA) was used for data analysis. Secondary analyses were performed for sex and medication status as the independent measures using ANOVA. For all analyses, $\alpha = 0.05$.

3. Results

We examined the expression of four isoforms of β-tubulin in the ACC (Fig. 1). There were no significant associations between expression of the isoforms of β-tubulin and age, pH, or PMI. A significant decrease in βI ($F(1,43) = 4.401$, $p<0.05$), but not in βII, βIII, or βIV protein expression was detected. No significant differences in VCP were detected.

The expression of βI, βII, βIII, βIV was also examined in the DLPFC (Fig. 2). We did not detect associations between expression of the isoforms of β-tubulin and age, pH, or PMI. A significant increase in βI ($F(1,43) = 14.79$, $p<0.001$), but not in βII, βIII, or βIV protein expression, was found. No significant differences in VCP were detected.

To determine if changes in the βI isoform were region specific, we also examined βI expression in the hippocampus (HC) and superior temporal gyrus (STG) (Fig. 3A–B). There were no significant associations between expression of βI and age, pH, or PMI in the HC or STG. No significant changes were detected in βI protein expression in these regions. No significant differences in VCP were detected.

The potential effects of antipsychotic medication and sex on the expression of the isoforms of β-tubulin were explored with post hoc statistical tests. A significant increase in βII protein expression ($F(2,49) = 7.32$, $p<0.05$) in the DLPFC, but not in the ACC, was detected in patients off of antipsychotic medication for at least 6 weeks prior to death, compared to patients on medications at the time of death as well as the comparison group (Fig. 4). No effect of medication status was found for βI, βIII, or βIV in the ACC or the DLPFC or for βI in the HC and STG (data not shown). No effect of sex on the expression of any of the isoforms of β-tubulin was detected in the ACC, DLPFC, HC, or STG (data not shown).

4. Discussion

We detected a significant increase in protein expression of βI-tubulin, but not βII, βIII, or βIV-tubulin, in the DLPFC. Western blot studies of β-tubulin protein expression using an antibody that

Table 1
Subject demographic information. Abbreviations: female (f), male (m), post mortem interval (PMI), antipsychotic drugs (APD). Values are presented as means ± standard deviation.

	ACC		STG		DLPFC		HC	
	Comparison	Schizophrenia	Comparison	Schizophrenia	Comparison	Schizophrenia	Comparison	Schizophrenia
N	27	31	25	23	29	35	22	21
Sex	11m/16f	21m/10f	14m/11f	16m/7f	13m/16f	24m/11f	11m/11f	15m/6f
Age (years)	77 ± 13.3	73 ± 11.1	79 ± 13	72 ± 12	78 ± 14	74 ± 11.6	77 ± 12	72 ± 12
Tissue pH	6.4 ± 0.2	6.3 ± 0.3	6.5 ± 0.2	6.4 ± 0.3	6.4 ± 0.3	6.4 ± 0.3	6.4 ± 0.2	6.4 ± 0.3
PMI (hours)	8.4 ± 7.1	12.6 ± 6.8	7.9 ± 7.1	14.6 ± 8.9	8.2 ± 7.1	12.5 ± 6.6	7.7 ± 6.9	14.5 ± 9.3
On/off APD	0/27	22/9	0/25	13/10	0/29	24/11	0/22	11/10

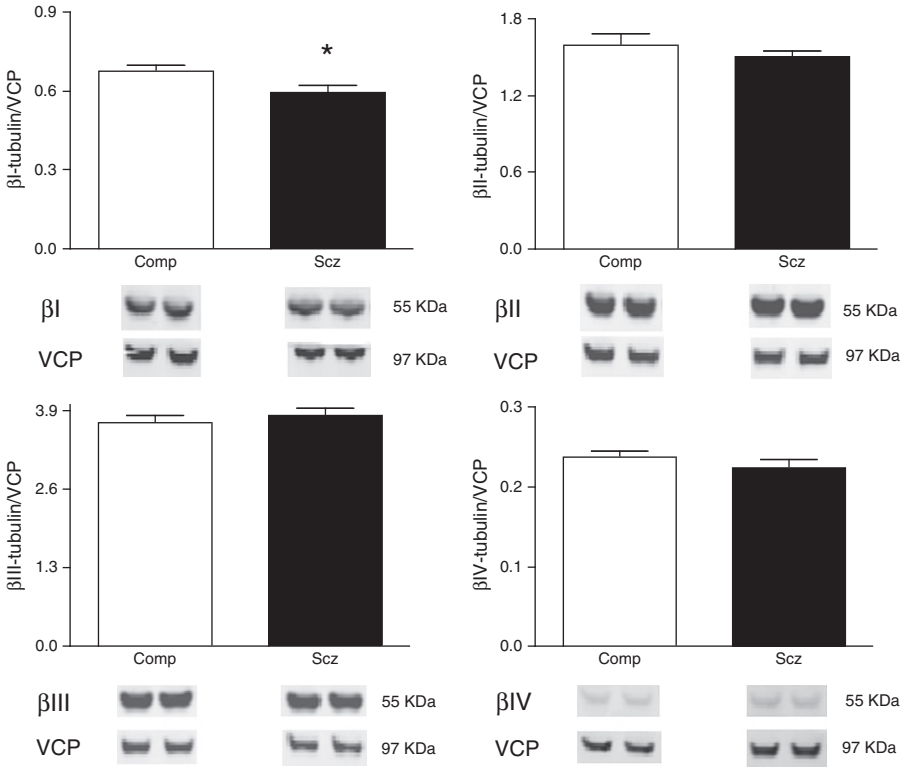

Fig. 1. Western blot analysis of the isoforms of β-tubulin normalized to VCP in ACC. Data are shown as mean ± standard deviation. Abbreviations: comparison group (comp); schizophrenia group (scz); valosin containing protein (VCP); kiloDalton (kDa); anterior cingulate cortex (ACC), *($p<0.05$).

detects all isoforms of β-tubulin did not detect changes in expression in the frontal cortex (Clinton et al., 2006; Bauer et al., 2009). On the other hand, studies utilizing mass spectrometry have found divergent changes in expression of pan-β-tubulin (Behan et al., 2009; English et al., 2009). One study found a significant increase of β-tubulin protein expression in a membrane associated fraction of cellular protein isolated from DLPFC gray matter in schizophrenia and bipolar disorder (Chan et al., 2011), while another study found a significant decrease of β-tubulin protein expression in tissue homogenate isolated from DLPFC-associated white matter in schizophrenia

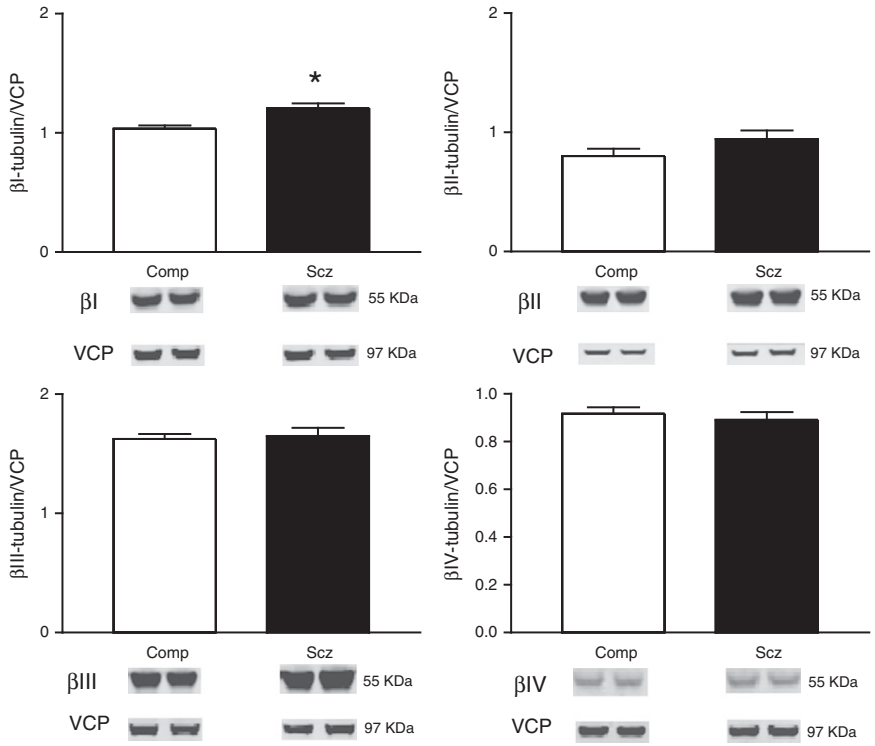

Fig. 2. Western blot analysis of the isoforms of β-tubulin normalized to VCP in DLPFC. Asterisks (*) indicate a significant value ($p<0.05$). Data are shown as mean ± standard deviation. Abbreviations: comparison group (comp); schizophrenia group (scz); valosin containing protein (VCP); kiloDalton (kDa); dorsolateral prefrontal cortex (DLPFC), *($p<0.05$).

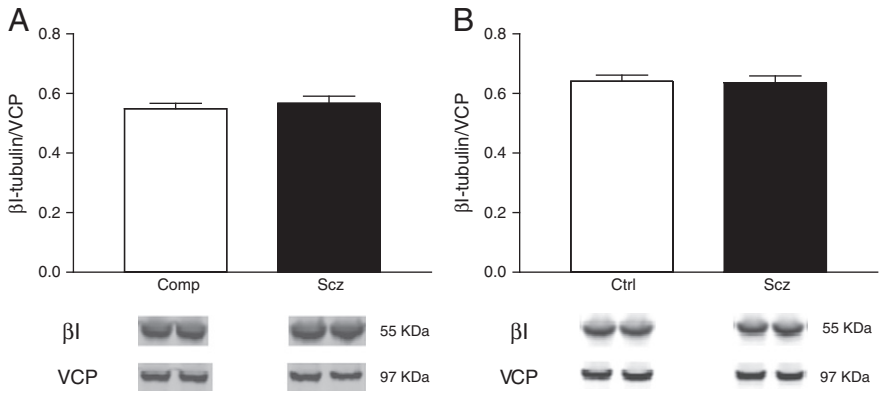

Fig. 3. Western blot analysis of βI-tubulin normalized to VCP in STG (A) and HC (B). No significant differences were observed. Data are shown as mean ± standard deviation. Abbreviations: comparison group (comp); schizophrenia group (scz); valosin containing protein (VCP); kiloDalton (kDa); hippocampus (HC); superior temporal gyrus (STG).

(Sivagnanasundaram et al., 2007), and a third found a decrease in βII tubulin protein expression in the ACC (Martins-de-Souza et al., 2010). These disparate findings might be due to differences in tissue, region, brain collection, and/or methodological approach. For example, we used western blotting with β-tubulin isoform-specific antisera to probe for differences in β-tubulin protein expression in individual subjects, while decreased βII tubulin protein expression in one study was detected using pooled samples, 2D gel electrophoresis, and mass spectrometry (Martins-de-Souza et al., 2010). Regardless of the valence of the changes, these data suggest that expression of tubulin isoforms may be abnormal in a region-specific manner in severe mental illnesses.

In contrast with our results in the DLPFC, we detected a significant decrease in βI-tubulin protein expression in ACC. Regionally divergent changes in gene expression are not without precedent. Several other studies have found an increase in various gene expression products in one area, and a decrease in another, suggesting that changes in the brain in schizophrenia are not global, but may be region specific (Bachus et al., 1997; Katsel et al., 2005a, 2005b; Kristiansen et al., 2006; Bauer et al., 2008; Oni-Orisan et al., 2008; Kristiansen et al., 2010). To explore the hypothesis that changes in βI-tubulin are regionally specific, we examined βI-tubulin protein expression in two other regions, the STG and HC. We found no significant changes in βI-tubulin in either the STG or the HC, suggesting that the changes in βI-tubulin are specific to the frontal cortex, consistent with reports of cytoskeletal alterations in these regions in schizophrenia (Black et al., 2004; English et al., 2009; Hayashi-Takagi et al., 2010).

Our data support a growing body of evidence suggesting abnormalities of the cytoskeleton in schizophrenia. Several schizophrenia susceptibility genes impact cytoskeletal composition. For example, neuregulin-1, and its receptor ErbB4, modulate dendritic spine density, control glutamatergic synapse maturation and plasticity, and may alter learning and memory (Li et al., 2007; Chen et al., 2008; Barros et al., 2009). DISC1, via an interacting protein Rac1, is an important factor for spine morphology (Hayashi-Takagi et al., 2010). Nogo-66-Receptor 1 (NGR) may alter axonal morphology in schizophrenia by inhibition of axon growth, while diminished levels of dysbindin are associated with decreased neurite outgrowth (Budel et al., 2008; Ghiani et al., 2010). Studies in postmortem brain tissue have also implicated cytoskeletal and interacting proteins in the etiology of schizophrenia (Prabakaran et al., 2004; Beasley et al., 2006; Clark et al., 2006; Behan et al., 2009; English et al., 2009; Martins-de-Souza et al., 2010). For example, decreased dendritic outgrowth was detected in the prefrontal and auditory cortices (Black et al., 2004; Sweet et al., 2009). Decreased dendritic outgrowth could alter neuronal functioning and contribute to the symptomology of schizophrenia. Taken together, these data support a hypothesis of cytoskeletal abnormalities in schizophrenia.

β-tubulin is commonly used as loading control for studies in schizophrenia (Clinton et al., 2006; Bauer et al., 2009; Ghose et al., 2009). Our western blot results suggest that use of pan-β-tubulin antibodies as a loading control for western blotting should be evaluated on a case by case basis, since there may be illness-specific changes in

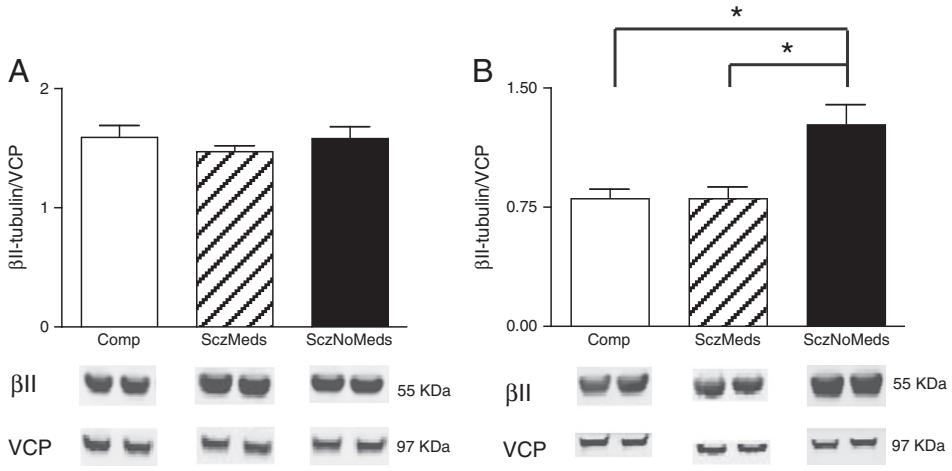

Fig. 4. Western blot analysis of βII-tubulin normalized to VCP in the ACC (A) and DLPFC (B). Schizophrenia patients were off medications for at least 6 weeks prior to death. Data are shown as mean ± standard deviation. Abbreviations: comparison group (comp); schizophrenia group subjects on medication (SczMeds); schizophrenia group subjects off medications (SczNoMeds); dorsolateral prefrontal cortex (DLPFC); anterior cingulate cortex (ACC), *($p<0.05$).

the expression of tubulin isoforms, which might impact pan-β-tubulin levels. If changes in β-tubulin are found, other proteins such as β-actin or valosin-containing protein may be considered for normalization of western blot studies (Bauer et al., 2009).

We found changes in βI-tubulin, but not βII, βIII, or βIV-tubulin, in schizophrenia, suggesting that this isoform may have a specific role(s) in the pathophysiology of this illness. We speculate that the selective involvement of the βI-isoform in schizophrenia is related to its ability to inhibit actin tubule formation, a process associated with cell division and differentiation (Guo et al., 2010). Patients with schizophrenia have decreased cell numbers and neuropil in some brain regions, consistent with attenuated cell divison and a loss of neuronal and astroglial processes (Selemon and Goldman-Rakic, 1999).

We found a higher level of protein expression for βI versus βII-tubulin in the ACC, and roughly equivalent levels in the DLPFC. A study examining the relative expression of tubulin isoform mRNAs found high levels of βI and βII in the brain, consistent with our findings (Lenadro-Garcia et al., 2010).

There are some technical limitations for this study. Since we utilized a group of elderly subjects, our data may not be applicable to earlier stages of this illness. However, we did not find a significant correlation between age and protein expression for any of the β-tubulin isoforms. In addition, we examined the expression of β-tubulin at a regional, but not a cellular level, which could mask cell specific changes in β-tubulin isoform expression. With the exception of increased βII-tubulin in subjects off antipsychotics for 6 weeks prior to death in the DLPFC, we did not detect an effect of antipsychotic medication on tubulin isoform expression in subjects with schizophrenia, consistent with previous studies which indicated that antipsychotics do not alter neuronal density or dendritic size (Selemon et al., 1999; Black et al., 2004).

In summary, the emerging functional roles of the tubulin isoforms will reveal the impact of isoform specific changes in pathophysiological states. Our findings support a growing literature that implicates abnormalities of cytoskeletal elements in severe mental illness.

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The funding sources for this manuscript had no role in the study design, data collection, data analysis, interpretation of the data, writing of the report, or the decision to submit the paper for publication.

Contributors

Mark Moehle performed the experiments, analyzed the data and wrote the first draft of the manuscript. All authors reviewed the manuscript prior to publication and contributed to the final version. Vaharam Haroutunian provided the tissue for the study. Richard Luduena provided the antisera. Robert McCullumsmith and James H. Meador-Woodruff supervised the study, the data collection, and data analysis and provided the laboratory infrastructure for the experiments.

Conflict of interest

Dr. Richard Luduena states that he has shares in Oncovista Innovative Therapies, 14785 Omicron Drive, Suite 104, San Antonio, TX 78245 and he serves as a consultant for the European Food Safety Authority. The other authors have nothing to disclose.

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