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Brief Report

Evaluation of the neuroprotective effect of antipsychotics by serum quantification of protein S100B

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ABSTRACT

Objective: This research delves into the intricate interplay between antipsychotic medications and neuroprotection focusing on the S100B protein—a central player in the regulation of neuroapoptotic activity.
Method: Blood samples were collected to assess serum S100B protein levels using an immunoassay of immunoelectrochemiluminescence. The first two samples were collected with a 3-month interval between each, and the third sample was obtained 6 months after the previous one. Changes in S100B protein levels throughout the study were assessed using Friedman's ANOVA test. This was followed by the Wilcoxon signed-rank test with Bonferroni correction to account for multiple comparisons.
Results: This study involved 40 patients diagnosed with severe mental disorders (34 schizophrenia, 4 schizoaffective disorder, 1 bipolar disorder, and 1 borderline personality disorder). These patients had been receiving antipsychotic treatment for an average duration of 17 years. The results revealed that the S100B protein remained within physiological levels (median values 39.0 ng/L for the first sample, median values 41.0 ng/L for the second sample, and median values 40.5 ng/L for the third sample) with no significant changes ($p = 0.287$), with all anti-psychotic medicaments values consistently below 50 ng/L, a lower value compared to maximum range of 105 ng/L. Importantly, there were no significant differences in S100B protein levels between patients on monotherapy and those on combination antipsychotic therapy ($p = 0.873$), suggesting that combination therapy did not increase neuroapoptotic activity.
Conclusions: These findings provide compelling evidence for the potential neuroprotective effects of long-term antipsychotic treatment in individuals with severe mental disorders. By maintaining physiological levels of the S100B protein, antipsychotic medications may help protect against neuronal damage and dysfunction. This research contributes valuable insights into the neuroprotective mechanisms of antipsychotic drugs, enhancing our understanding of their potential benefits in the treatment of severe mental disorders.

Evaluación del efecto neuroprotector de los antipsicóticos mediante la cuantificación sérica de la proteína S100B

Palabras clave:
S100B
Esquizofrenia
Antipsicótico
Efectos neuroprotectores

RESUMEN

Objetivo: Esta investigación explora la compleja interacción entre los medicamentos antipsicóticos y la neuroprotección, enfocándose en la proteína S100B, un actor central en la regulación de la actividad neuroapoptótica.
Método: Se recolectaron muestras de sangre para evaluar los niveles séricos de la proteína S100B utilizando un inmunoensayo de inmunoelectroquimioluminiscencia. Las dos primeras muestras se recogieron con un intervalo

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de 3 meses entre cada una, y la tercera muestra se obtuvo 6 meses después de la anterior. Los cambios en los niveles de la proteína S100B a lo largo del estudio se evaluaron utilizando la prueba ANOVA de Friedman. Posteriormente, se realizó la prueba de rango con signo de Wilcoxon con corrección de Bonferroni para tener en cuenta las múltiples comparaciones.

Resultados: Este estudio involucró a 40 pacientes diagnosticados con trastornos mentales graves (34 con esquizofrenia, 4 con trastorno esquizoafectivo, 1 con trastorno bipolar y 1 con trastorno límite de la personalidad). Estos pacientes habían estado recibiendo tratamiento antipsicótico durante una duración promedio de 17 años. Los resultados revelaron que la proteína S100B se mantuvo dentro de niveles fisiológicos (mediana de 39.0 ng/L para la primera muestra, mediana de 41.0 ng/L para la segunda muestra, y mediana de 40.5 ng/L para la tercera muestra) sin cambios significativos ($p = 0.287$), con todos los valores de los medicamentos antipsicóticos consistentemente por debajo de 50 ng/L, un valor inferior comparado con el rango máximo de 105 ng/L. Es importante destacar que no hubo diferencias significativas en los niveles de la proteína S100B entre los pacientes en monoterapia y aquellos en terapia combinada con antipsicóticos ($p = 0.873$), lo que sugiere que la terapia combinada no aumentó la actividad neuroapoptótica.

Conclusiones: Estos hallazgos proporcionan evidencia convincente de los posibles efectos neuroprotectores del tratamiento antipsicótico a largo plazo en individuos con trastornos mentales graves. Al mantener niveles fisiológicos de la proteína S100B, los medicamentos antipsicóticos pueden ayudar a proteger contra el daño y la disfunción neuronal. Esta investigación aporta valiosos conocimientos sobre los mecanismos neuroprotectores de los medicamentos antipsicóticos, mejorando nuestra comprensión de sus posibles beneficios en el tratamiento de trastornos mentales graves.

This study sheds light on the neuroprotective potential of long-term antipsychotic treatment in severe mental disorders, indicating that it helps maintain physiological levels of the S100B protein, thus potentially safeguarding against neuronal damage and dysfunction. These findings offer valuable insights into the neuroprotective mechanisms of antipsychotic drugs.

Introduction

Antipsychotic drugs are commonly used to treat individuals with severe mental disorders, such as schizophrenia or bipolar disorder, with the aim of reducing the frequency and severity of psychotic episodes. The spectrum of available antipsychotic medications is extensive, and in cases where a single antipsychotic proves ineffective, a combination of several may be necessary. Numerous studies have attributed neuroprotective effects to antipsychotic drugs, as they have been observed to shield against cellular apoptosis, potentially slowing the progression of the disease.[1]

Neuroapoptosis refers to the programmed cell death of damaged or dysfunctional neurons. Several studies have established a connection between increased serum concentrations of the S100B protein and heightened neuroapoptotic activity as well as brain damage.[2–4] S100B is an abundant protein found in the brain, primarily localized in astrocytes. It is released into the extracellular space following neuronal death. Notably, the effects of the S100B protein can be either neurotoxic or neurotrophic, depending on its concentration. At low physiological concentrations, it seems to exert a neurotrophic or protective effect by promoting neuronal growth and enhancing their survival.

Conversely, at high concentrations, the S100B protein exerts a neurotoxic effect by triggering neuroapoptosis through the activation of proinflammatory cytokines that ultimately result in cell death.[5] Indeed, protein S100B has garnered attention as a potential marker for assessing neurotoxic effects resulting from various treatments.[6] Interestingly, certain studies have reported a significant reduction in serum levels of S100B protein after several weeks of antipsychotic treatment. However, it's important to note that in the meta-analysis conducted by Schroeter et al., serum concentrations of S100B protein were found to be higher in patients with schizophrenia compared to healthy individuals, and these levels did not show a significant decrease even after 7 weeks of antipsychotic treatment.[7] Therefore, this study aimed to assess the intricate interplay between antipsychotic medications and neuroprotection focusing on the S100B protein—a central player in the regulation of neuroapoptotic activity.

Methods

In this cross-sectional observational study with a prospective patients recruitment, we conducted an assessment of the potential neuroprotective effect resulting from antipsychotic treatment by measuring the serum levels of the S100B protein. Participants were recruited from the Mental Health Therapeutic Community at the University Hospital of Puerto Real (Cádiz, Spain), which can accommodate up to 40 residents at a time. Therefore, assuming a statistical significance level and a contrast power of 70% (with Yates correction), we find that the sample size will be sufficient. The calculation of the sample size has been performed using Epidat 3.1, available at: http://lcsilva.sbhac.net/Otros/Epidat/epidat.html. Participants must meet the following inclusion criteria: diagnosis of a severe mental disorder and adulthood. Exclusion criteria include the inability to read, understand, or respond to study-related questions, as well as a lack of willingness to participate. All potential participants were invited to an informative session where they were presented with details about the study. Those who expressed interest in participating were asked to sign an informed consent form. This study was approved by the Research Ethics Committee of Cádiz. Patients were previously diagnosed with their mental state before the beginning of the study.

All patients completed the Positive and Negative Syndrome Scale (PANSS).[8,9] This scale comprises 30 items designed to assess the schizophrenic syndrome from a dual-dimensional perspective, evaluating the severity of positive, negative, and general syndrome symptoms. Each item is rated on a Likert scale ranging from 1 (absence of the symptom) to 7 (extreme severity), resulting in scores ranging from 7 to 49 for positive and negative scales, and from 16 to 112 for general psychopathology. The scale can encompass both positive and negative valences, with scores ranging between −42 and +42. There are no predefined cutoff points for the scores obtained; instead, direct scores are represented. The PANSS must be administered by a clinician using a semi-structured interview technique and remains one of the most widely used instruments in both clinical practice and research.

To quantify serum levels of the S100B protein, three blood samples were collected from each patient from a peripheral venous source. We utilized an immunoassay of immunoelectrochemiluminescence on the Hitachi Cobas Modular E-170 autoanalyzer (Roche Diagnostics,

Rotkreuz, Switzerland) for this purpose. The reference values for healthy individuals typically range from 5 to 105 ng/L. The first two samples were collected with a 3-month interval between each as a long enough period to observe short-term changes in the levels of the S100B protein through the use of the medication. The third sample was obtained 6 months after the previous one, serving as a measurement for long-term effects, approximately 9 months after the initial measurement.

The Kolmogorov-Smirmov test was used to check the normality of distribution. Outcomes are presented as means ± standard deviations, if the variables do not comply with a normal distribution, they showed with the median (minimum value-maximum value). Changes in S100B protein throughout the study were assessed using Friedman's ANOVA test followed by the Wilcoxon signed-rank test with Bonferroni correction for post-hoc comparisons between different measurement time points. These S100B protein values were subsequently compared between groups using a Mann–Whitney U-test.

All statistical analyses were conducted using IBM SPSS Statistics version 25 software (SPSS Inc., Chicago, IL, United States of America). The significance level was set at $p < 0.05$ to determine statistical significance, and when the Bonferroni correction was applied it was set at $p < 0.017$ (0.05 / number of comparisons).

Results

Our study included 40 patients, with ages ranging from 22 to 55 years (mean = 38.15 years). Among these patients, there were 10 women and 30 men, all diagnosed with severe mental disorders. Specifically, 34 patients had been diagnosed with schizophrenia in one of its clinical forms, 4 with schizoaffective disorder, 1 with bipolar disorder, and 1 with borderline personality disorder. The duration of antipsychotic treatment for these patients extended for at least 3 years, with an average treatment duration of 17 years.

Of the 40 patients, 12 were receiving monotherapy with a single antipsychotic, while 28 were on combination antipsychotic therapy. Among those on combination therapy, 17 were taking two antipsychotics, 10 were taking three, and 1 patient was taking four different antipsychotic medications.

The mean body mass index of the 40 patients fell within the pre-obese range (28.29 ± 5.1 kg/m^2). The data from the Positive and Negative Syndrome Scale showed a mean value of 32.23 ± 6.01 points for the positive scale, 38.36 ± 6.26 points for the negative scale and 71.91 ± 11.73 points for the general scale.

The results obtained are summarized in Table 1 and Table 2. Across all the antipsychotics studied the medians of serum levels of the S100B protein showed no significant variations ($p = 0.287$) in the three samples analyzed ($p = 0.605$ between 1st and 2nd sample, $p = 0.655$ between 2nd and 3rd sample, and $p = 0.342$ between 1st and 3rd sample), with all anti-psychotic drugs values consistently below 50 ng/L, a lower value compared to maximum range of 105 ng/L. The mean value of serum concentration of the S100B protein in the three samples ranged between 22 and 96 ng/L. The median of the mean value for the three samples across all patients indicated a low concentration of the S100B protein (40.5 ng/L). Furthermore, no significant differences were found in serum levels of the S100B protein between patients receiving monotherapy and those on combination antipsychotic treatment ($p = 0.873$).

Discussion

The results from this study suggest that the serum of the patients in our study contained normal physiological concentrations of the S100B protein, indicating preserved neuroapoptotic activity and supporting the potential neuroprotective effect of antipsychotic treatment. In addition to this, the lack of significant differences found in the levels of serum S100B protein suggests that combined antipsychotic therapy did not increase neuroapoptotic activity or a neuroprotective effect.

It has been shown that the levels of serum S100B protein are elevated in patients with mental disorders, mainly schizophrenia, compared to healthy individuals.[7] In fact, the level of S100B in adult patients is considered a marker of response to treatment.[10] This could be attributed to the dynamic glial alterations produced by the disease.[11] In the context of schizophrenia, dystrophy and swelling of the astrocytes (which contain the protein S100B) may release the protein under reduced energy supply or cell damage which may increase the levels of this protein in these patients.[12] Interestingly, our results appear to contrast with previous research, which has often indicated elevated levels of S100B protein in individuals with mental disorders, especially schizophrenia, when compared to healthy individuals. The results from our study showed that medicated patients had normal physiological levels of the protein S100B, which contradicts the data from previous authors.[7] This diference in the results could be attributed to the treatment as patients taking neuroleptic/antipsychotic medication for a longer time tend to be less symptomatic compared to recent-onset schizophrenia, thus showing lower PANSS scores but possibly also elevated S100B levels with longer duration of illness.[12] For this reason, biomarker values of S100B are not specific to the diagnosis of schizophrenia, but they may be a potential factor in predicting symptom severity and the degree of brain damage and glial dysfunction.[13] Following this, the results from this study are quite noteworthy, as the treatment did not result in a significant increase in this protein. This suggests that both mono and polytreatment are safe options for mental disorder patients in terms of brain damage and glial dysfunction and should be focused on the desired therapeutic effects. However, it is worth mentioning that while polytreatment may appear to be a safe option, the primary objective should be to treat patients with the minimum necessary medications. Polypharmacy should be considered only when a single medication cannot achieve all the beneficial effects required for the patient's condition.

Nonetheless, it's essential to note that a meta-regression analysis conducted by Schümber et al. suggests a trend toward a reduction in serum S100B levels through medication, supporting the potential therapeutic impact of antipsychotic treatments. Our findings add to this evolving body of knowledge, suggesting that appropriately medicated patients with mental disorders, can attain serum S100B protein levels within the normal physiological range.

Table 1
Serum levels of S100B protein in patients with severe mental disorder.

Patients		N	Serum levels of S100B protein (ng/L)			
			1st sample	2nd sample*	3rd sample**	Mean 9-month value
All patients		40	39.0 (16–165)	41.0 (18–106)	40.5 (24–119)	40.5 (22–96)
Gender:	Women	10	36.0 (16–97)	44.5 (24–72)	46.0 (27–119)	44.0 (22–78)
	Men	30	39.5 (18–165)	40.0 (18–106)	40.5 (24–97)	39.5 (23–96)
Pathology	Schizophrenia	34	40.0 (16–97)	43.0 (18–72)	42.0 (26–72)	41.0 (22–78)
	Schizoaffective disorder	4	37.0 (18–165)	40.0 (22–106)	10.0 (24–119)	38.0 (22–96)
	Bipolar disorder	1	36	38	39	37
	Boderline personality disorder	1	39	40	41	40

Values are shown as median (minimum value-maximum value). *2nd sample after 3 months of the first sample. **3rd sample 6 months after the 2nd sample.

Table 2
Serum levels of S100B protein in patients with severe mental disorder depending on their treatment.

Patients		N	Serum levels of S100B protein (ng/L)			
			1st sample	2nd sample*	3rd sample**	Mean 9-month value
All patients		40	39.0 (16–165)	41.0 (18–106)	40.5 (24–119)	40.5 (22–96)
Treatment:	Monotherapy	12	39.0 (16–97)	40.5 (18–72)	47.5 (27–97)	43.0 (22–78)
	Combination antipsychotic therapy	28	39.0 (18–165)	41.0 (22–106)	39.0 (24–119)	39.0 (23–96)
Drugs:	Oral Aripiprazole	10	40.0 (18–69)	41.0 (27–106)	45.5 (33–85)	47.0 (28–74)
	Intramuscular Aripiprazole	7	45.0 (30–74)	49.0 (31–78)	48.0 (30–85)	47.0 (32–74)
	Asenapine	4	41.0 (30–57)	38.5 (36–54)	35.5 (30–53)	40.0 (32–51)
	Clothiapine	3	39.0 (25–64)	30.0 (27–52)	44.0 (33–65)	38.0 (28–60)
	Clozapine	21	39.0 (16–165)	43.0 (18–106)	41 (24–119)	40.0 (22–96)
	Haloperidol	2	46.5 (29–64)	46.5 (41–52)	47.0 (29–65)	46.5 (33–60)
	Olanzapine	5	36.0 (33–104)	49.0 (35–78)	44.0 (32–119)	42.0 (38–73)
	Paliperidone	21	40.0 (20–165)	40.0 (22–87)	39.0 (24–119)	40.0 (23–96)
	Quetiapine	3	31.0 (29–34)	29.0 (27–41)	29.0 (26–39)	30.0 (29–33)
	Oral Risperidone	3	39.0 (30–104)	32.0 (30–48)	39.0 (39–44)	38.0 (34–64)
	Intramuscular Risperidone	2	32.5 (29–36)	38.0 (35–41)	36.5 (29–44)	35.5 (33–38)
	Zuclopenthixol	1	31	29	39	33

Values are shown as median (minimum value-maximum value). *2nd sample after 3 months of the first sample. **3rd sample 6 months after the 2nd sample.

Interestingly, we observed that normal physiological levels of the S100B protein were achieved in both patients who underwent monotherapy and those who received a combination of medications. This finding holds particular relevance as it suggests that polypharmacy, the use of multiple medications, does not appear to influence the levels of the S100B protein. This lack of influence on S100B protein levels may be associated with a potential reduction in neuroapoptotic activity as well as brain damage.[2–4]

This study is not without limitations. Despite reaching the maximum possible number of 40 participants within the hospital, this sample size may not be sufficient to generalize the findings to the entire population with mental disorders. Additionally, being a cohort study, causal relationships cannot be established. Furthermore, this study did not investigate other aspects related to neuroprotection and mental disorders, such as the effects of longer treatment duration or treatment discontinuation on S100b protein levels. Further research is necessary to address these questions and provide more comprehensive insights into the topic.

In conclusion, our study revealed that patients with severe mental disorders who had been undergoing antipsychotic treatment for an extended duration exhibited normal physiological serum levels of the S100B protein. These findings provide valuable evidence supporting the notion of a potential neuroprotective effect associated with long-term antipsychotic treatments.

Authors contributions

JDS conceptualized the study. COG, PL, CCS, and JCP conducted the investigation. JDS and JCP drafted the initial manuscript, and all authors reviewed and revised it.

Conflict of interest

The authors claimed no conflict of interest.

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Ethical considerations

This clinical study adhered to international ethical recommendations in strict accordance with the protocol and principles delineated in the current revised version of the Helsinki Declaration. Additionally, the study followed applicable regulatory requirements, particularly aligning with the ICH Tripartite Guideline “Good Clinical Practice.” Prior to the commencement of the study, the principal investigator diligently sought and obtained timely approval and authorization from the Clinical Research Ethics Committee. This commitment to ethical oversight ensures the protection of participants' rights, safety, and well-being throughout the course of the research.

CRediT authorship contribution statement

José D. Santotoribio: Writing – original draft, Investigation, Data curation, Conceptualization. **Pilar Lozano:** Writing – review & editing, Investigation, Formal analysis. **Consuelo Cañavate-Solano:** Writing – review & editing, Methodology, Investigation. **Juan Corral-Pérez:** Writing – review & editing, Investigation, Conceptualization. **Cristina O'Ferrall-González:** Writing – review & editing, Formal analysis, Conceptualization.

References

1. Zeng Z, Wang X, Bhardwaj SK, Zhou X, Little PJ, Quirion R, et al. The Atypical Antipsychotic Agent, Clozapine, Protects Against Corticosterone-Induced Death of PC12 Cells by Regulating the Akt/FoxO3a Signaling Pathway. Mol Neurobiol. 2017;54(5):3395–406. doi: 10.1007/s12035-016-9904-4.
2. Santotoribio JD, Cañavate-Solano C, Quintero-Prado R, González-Macías C, Soto-Pazos E, Vilar-Sanchez Á, et al. Neuroapoptosis in newborns with respiratory acidosis at birth. Clin Biochem. 2019;74:69–72. doi: 10.1016/j.clinbiochem.2019.08.013.
3. Ramos Ramos V, Mesa Suárez P, Santotoribio JD, González García MÁ, Muñoz Hoyos A. Neuroprotective effect of sevoflurane in general anaesthesia. Med Clin (Barc). 2017;148(4):158–60. doi: 10.1016/j.medcli.2016.10.039.
4. Mesa Suárez P, Santotoribio JD, Ramos Ramos V, González García MÁ, Pérez Ramos S, Portilla Huertas D, et al. Brain damage after general anesthesia. Med Clin (Barc). 2016;146(9):384–8. doi: 10.1016/j.medcli.2016.01.018.
5. Donato R, Heizmann CW. S100B Protein in the Nervous System and Cardiovascular Apparatus in Normal and Pathological Conditions. Cardiovasc Psychiatry Neurol 2010;2010:929712. doi: 10.1155/2010/929712.
6. Santotoribio JD, Parodi Fernández V, Mesa Suárez P. Sedation with midazolam without neurotoxic effects. Med Clin (Barc). 2018;150(11):450. doi: 10.1016/j.medcli.2017.10.029.
7. Schroeter ML, Abdul-Khaliq H, Krebs M, Diefenbacher A, Blasig IE. Neuron-specific enolase is unaltered whereas S100B is elevated in serum of patients with schizophrenia — Original research and meta-analysis. Psychiatry Res 2009;167(1–2):66–72. doi: 10.1016/j.psychres.2008.01.002.
8. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophr Bull 1987;13(2):261–76. doi:10.1093/schbul/13.2.261.
9. Gil D, Bengochea R, Arrieta M, Fernández M, Álvarez A, Sánchez R, et al. Validez del factor cognitivo de la PANSS como medida del rendimiento cognitivo en esquizofrenia. Rev Psiquiatr Salud Ment 2009;2(4):160–8. doi: 10.1016/S1888-9891(09)73234-3.
10. Bilginer C, Yaman H, Karadeniz S, Hızarcı Bulut S, Ozer Yaman S, Aydogdu S. Oxidative Stress and Serum S100B Levels in Adolescents with First-Episode Drug-Naive Unipolar Depression. Psychiatr Danub. 2021;33(2):158–64. doi: 10.24869/psyd.2021.158.

11. Schümberg K, Polyakova M, Steiner J, Schroeter ML. Serum S100B Is Related to Illness Duration and Clinical Symptoms in Schizophrenia—A Meta-Regression Analysis. Front Cell Neurosci 2016;(10):46. doi: 10.3389/fncel.2016.00046.
12. Steiner J, Bernstein HG, Bogerts B, Gos T, Richter-Landsberg C, Wunderlich MT, et al. S100B is expressed in, and released from, OLN-93 oligodendrocytes: Influence of serum and glucose deprivation. Neuroscience. 2008;154(2):496–503. doi: 10.1016/j.neuroscience.2008.03.060.
13. Hong W, Zhao M, Li H, Peng F, Wang F, Li N, et al. Higher Plasma S100B Concentrations in Schizophrenia Patients, and Dependently Associated with Inflammatory Markers. Sci Rep 2016;6:27584. doi: 10.1038/srep27584.