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The Relationship Between Pregabalin and ADNP in Experimental Spinal Cord Injury

Deneysel Spinal Kord Hasarında Pregabalin ve ADNP İlişkisi

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ABSTRACT

Aim: The two main forms of traumatic spinal cord injury exist. The first type of injury occurs when mechanical forces compress blood vessels and damage both axons and neural membranes. The second type of injury occurs through pathophysiological and metabolic processes which start after the initial damage. Glutamate over-expression is an important secondary injury mechanism. We examined pregabalin's neuroprotective effect on ADNP (Activity Dependent Neuroprotective Factor) levels in a rat spinal cord injury model.

Methods: The fourth Wistar male rats received random assignments to five distinct groups: the 1. grup (no any surgical approach), 2. group (laminectomy only), 3. group (spinal cord injury without medication), 4. group (spinal cord injury and the methylprednisolone treated), 5. group (spinal cord injury and the pregabaline treated group). Spinal cord injury was produced by climp compression. Functional evaluations were done using the inclined plane test and criteria of Drummond and Moore, evaluation of blood levels and tissue levels of ADNP were done by ELISA, and Immunohistochemistry. The glial cells and neural cells evaluated by Hematoxylin and eosin staining of tissue.

Results: The results showed no important variations in motor function between different spinal cord injury groups (p=0.053). The pregabalin group had significantly higher neural cell counts (9.68 ± 3.58) than both group 3 (5.06 ± 2.55) and group 4 (6.80 ± 2.59) (p<0.01). The pregabalin group showed the highest glial cell numbers at 41.15 ± 12.12 compared to all other treatment groups (p<0.01). The ADNP levels in the pregabalin group reached 2.739 ± 0.383 but failed to reach statistical significance (p=0.085).

Conclusion: This experiment demonstrates that it can act as a neuroprotector in rats after SCI due to the high level of nerve cells and glial cells.

Keywords: Spinal cord, rat, pregabaline, ADNP

ÖZ

Amaç: Travmatik omurilik yaralanmasının iki ana türü vardır. İlk tür yaralanma, mekanik kuvvetlerin kan damarlarını sıkıştırması ve hem aksonları hem de sinir zarlarını hasarlaması sonucu meydana gelir. İkinci tür yaralanma ise, ilk hasarın ardından başlayan patofizyolojik ve metabolik süreçler sonucu meydana gelir. Glutamatın aşırı ekspresyonu, önemli bir ikincil yaralanma mekanizmasıdır. Sıçan omurilik yaralanması modelinde pregabalin'in ADNP (Aktiviteye Bağlı Nöroprotektif Faktör) düzeyleri üzerindeki nöroprotektif etkisini inceledik.

Yöntemler: Dördüncü Wistar erkek sıçanlar rastgele beş farklı gruba ayrıldı: 1. grup (cerrahi müdahale yapılmayan), 2. grup (sadece laminektomi yapılan), 3. grup (ilaçsız omurilik yaralanması), 4. grup (omurilik yaralanması ve metilprednizolon tedavisi uygulanan), 5. grup (omurilik yaralanması ve pregabalin tedavisi uygulanan). Omurilik yaralanması, klempleme kompresyonu ile oluşturuldu. Fonksiyonel değerlendirmeler eğimli düzlem testi ve Drummond ve Moore kriterleri kullanılarak yapıldı, kan ve doku seviyelerindeki ADNP değerlendirmeleri ELISA ve immünohistokimya ile yapıldı. Glial hücreler ve nöral hücreler, dokunun hematoksilen ve eozin boyaması ile değerlendirildi.

Bulgular: Sonuçlar, farklı omurilik yaralanması grupları arasında motor fonksiyonda önemli bir farklılık olmadığını gösterdi (p=0,053). Pregabalin grubu, hem grup 3 (5,06 ± 2,55) hem de grup 4 (6,80 ± 2,59) ile karşılaştırıldığında anlamlı olarak daha yüksek nöral hücre sayısına sahipti (9,68 ± 3,58) (p<0,01). Pregabalin grubu, diğer tüm tedavi gruplarına kıyasla 41,15 ± 12,12 ile en yüksek glial hücre sayısını gösterdi (p<0,01). Pregabalin grubundaki ADNP düzeyleri 2,739 ± 0,383'e ulaştı, ancak istatistiksel olarak anlamlı değildi (p=0,085).

Sonuç: Bu deney, yüksek düzeyde sinir hücresi ve glial hücre nedeniyle sıçanlarda SCI sonrası nöroprotektör görevi görebildiğini göstermektedir.

Anahtar kelimeler: Omurilik, Rat, pregabalin, ADNP

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Introduction

Spinal cord injury (SCI) represents a major public health issue globally because it results in permanent neurological deficits after 40-80 new cases per million per year occur annually [1]. The initial mechanical damage to the brain triggers a series of secondary damage processes which include excitotoxicity and oxidative stress and inflammation and apoptosis to cause progressive neurological decline [2]. The formation of glial scar tissue because of reactive astrocytosis and microglial activation creates barriers to functional recovery by preventing axonal regeneration [3].

The accepted standard treatment for spinal cord injury involves methylprednisolone administration which works to restrict secondary tissue damage through its anti-inflammatory and antioxidant properties. The NASCIS III study alongside various meta-analyses show that methylprednisolone treatment provides restricted benefits but generates significant adverse reactions [4]. This situation highlights the need to develop alternative neuroprotective strategies.

Pregabalin and gabapentin interact with voltage-dependent calcium channels through their binding to the α2-δ subunit to create a neuromodulatory effect on the nervous system while effectively treating neuropathic pain [5]. Research studies conducted recently show pregabalin provides neuroprotection in addition to its pain relief capabilities [6]. The neuroprotective effects of pregabalin occur through its ability to decrease glutamate release and microglial activation which safeguards neurons from excitotoxic cell death [7]. The exact mechanisms through which pregabalin protects neurons in SCI models have not been fully understood.

The transcription factor activity-dependent neuroprotective protein (ADNP) serves as a fundamental regulator of neuronal development and protection mechanisms. The body produces ADNP during neurotrauma to perform two main functions which include microtubule stabilization and prevention of cell death [8, 9]. The NAP peptide which stems from ADNP has shown promise in promoting recovery of functions in experimental SCI models [10]. The calcium channel modulation of pregabalin and calcium sensitivity of ADNP led us to predict that pregab impact on spinal cord injury recovery through motor function assessment and tissue examination and ADNP protein expression in ratalin would protect neurons through its effects on the ADNP pathway.

The research investigated pregabalin's models. The research predicted pregabalin would protect neurons through increased ADNP expression which would maintain neuronal structure after spinal cord injury. Research into this mechanism could reveal ADNP as a new therapeutic approach for spinal cord injury treatment.

Method

Study Population and Sample

This experimental study was conducted between November and December 2016 in a prospective randomised controlled design with the approval of the Akdeniz University Faculty of Medicine Animal Ethics Committee (Date: 03.10.2016, Decision No: 78, Protocol No: 2016.10.04). Power analysis determined a minimum of 8 subjects per group at 80% power and a 0.05 significance level [11]. A total of 40 male Wistar rats (250-300 g, 12-16 weeks old) were randomly divided into five groups. The study included male Wistar rats between 12-16 weeks old who weighed 250-300 grams and showed normal motor function at baseline (Drummond-Moore score ≥4) and no evidence of systemic diseases. The study excluded rats who showed neurological deficits before the study or had active infections or abnormal motor function at baseline or lost more than 20% of their body weight during the study or experienced surgical complications such as excessive bleeding or anesthesia-related death [11]. Motor function was assessed using the Drummond-Moore scale and the inclined plane test, while neuroprotective efficacy was evaluated by ADNP expression levels.

Study Procedures

Experimental animals were housed under standard laboratory conditions at 20–24°C and 45–65% humidity, with a 12-hour light-dark cycle [12]. Four rats were housed per cage with ad libitum access to chow and water. The basal motor functions and weights of all animals were recorded prior

to surgical intervention. During the postoperative period, manual bladder emptying was performed twice daily (at 08:00 and 20:00), and daily dressing changes and analgesic medication were administered [13]. The researchers conducted the inclined plane test and motor function scoring at 10:00 every day throughout the seven-day follow-up period to maintain measurement consistency. Sacrifice was performed on postoperative day 7 under intraperitoneal anaesthesia with ketamine (50 mg/kg) and xylazine (5 mg/kg), followed by intracardiac blood sampling and perfusion fixation [14]. Serum samples were centrifuged at 3000 rpm for 10 minutes and stored at -80°C until ELISA analysis [15]. Spinal cord tissues were excised in 2 cm segments 1 cm proximal and 1 cm distal to the lesion centre and fixed in 10% formaldehyde solution for 48 hours before histopathological processing.

Intervention Protocol

Five groups were formed in the study: Group 1 was the control group (n=8, no surgical intervention), Group 2 was the laminectomy group (n=8, T8-10 laminectomy only), Group 3 was the spinal cord injury group (n=8, laminectomy + clip compression at the T9 level), Group 4 methylprednisolone treatment group (n=8, injury + 30 mg/kg methylprednisolone), Group 5 pregabalin treatment group (n=8, injury + 50 mg/kg pregabalin). Randomisation was performed using a computer-assisted random number generator [13]. Surgical procedures were performed by the same surgeon using standardised techniques. Following a midline incision between thoracic vertebrae 8-10, the paravertebral muscles were dissected and laminectomy was performed. Spinal cord injury was created by applying compression at the T9 level for 10 seconds using a modified Aneurysm clip (70 grams closure force) [15]. In the treatment groups, medications were administered according to the following schedule:

Table 1. Drug Administration Timeline - Time 0: Spinal cord injury induction - 30 minutes post-injury: First dose (methylprednisolone 30 mg/kg or pregabalin 50 mg/kg i.p.) - 12 hours post-injury: Second dose - 24 hours post-injury: Third dose - 36 hours post-injury: Fourth dose - 48 hours post-injury: Fifth and final dose

All drugs were administered intraperitoneally by the same researcher to ensure consistency. The control and laminectomy groups received equivalent volumes of saline at the same time points.

Statistical Analysis

Data analysis was performed using the SPSS 22.0 software package. Descriptive statistics were presented as mean (SD), median, and minimum-maximum values. For continuous variables showing a normal distribution, one-way analysis of variance (ANOVA) was used for intergroup comparisons, and the Sidak test was used for post-hoc pairwise comparisons. The Kruskal-Wallis H test was used for non-normally distributed or ordinal data, and the Mann-Whitney U test was used for pairwise comparisons. Weight loss percentages were calculated using the formula (initial weight - final weight)/initial weight. For histological counts, neurons and glial cells entering the standard digital camera image field at 40X magnification were counted, and the neuron/total cell ratio was determined as a percentage. The ELISA procedures followed the instructions provided by the manufacturer in the kit catalog number. The analysis included two duplicate runs for each sample. ELISA absorbance values were measured at 450 nm wavelength, and intergroup comparisons were performed using the ANOVA test. A $P<0.05$ value was considered statistically significant. No imputation was applied as there was no missing data.

Results

The inclined plane test and Drummond-Moore scoring system assessed motor function in this study. Control animals achieved the highest angle values (74.20 ± 4.45°) while laminectomy-only subjects achieved 66.79 ± 6.21°. The spinal cord injury groups showed decreased inclined plane performance (Group 3: 49.20 ± 5.32°, Group 4: 50.45 ± 4.78°, Group 5: 51.61 ± 5.91°) with no statistically significant difference between treatment groups ($p>0.05$). Drummond-Moore scores were 4.00 (median) for control and laminectomy groups, and 1.00–2.00 (median) for all spinal cord injury groups (Table 1).

The histopathological analysis showed that

different cell types existed between the research groups. The control group displayed normal spinal cord tissue with intact neuronal architecture. The laminectomy group maintained their neurons at levels which were similar to those of the control group. The neuron counts for Group 3 (SCI only) were 5.06 ± 2.55 per high-power field while Group 4 (methylprednisolone) had 6.80 ± 2.59 and Group 5 (pregabalin) had 9.68 ± 3.58 ($p<0.001$). The glial cell numbers were as follows: Group 1 (control) 15.23 ± 4.12, Group 2 (laminectomy) 18.45 ± 5.23, Group 3 (SCI) 28.34 ± 6.78, Group 4 (methylprednisolone) 32.56 ± 8.34, and Group 5 (pregabalin) 41.15 ± 12.12 ($p<0.001$). The neuron-to-total-cell ratio in controls was 32.61 ± 9.34% but it decreased to 13.02 ± 6.54% in Group 3 and 20.52 ± 7.96% in Group 4 and 21.14 ± 10.35% in Group 5 ($p<0.001$) (Figure 1, Table 2).

Table 1. Functional Assessment Parameters

Group	n	Inclined Plane Test (°) Mean ± SD	Motor Function Score Median (Min–Max)
Control (1)	8	74.20 ± 4.45	4.00 (4–4)
Laminectomy (2)	8	66.79 ± 6.21	4.00 (3–4)
Spinal Cord Injury (3)	8	49.20 ± 3.27	1.50 (0–3)
SCI + Methylprednisolone (4)	8	51.61 ± 5.57	1.00 (1–3)
SCI + Pregabalin (5)	8	51.61 ± 5.32	2.00 (1–3)
Statistical Analysis		F = 270.73; p < 0.001*	χ^2 = 27.84; p < 0.001*
Post-hoc Comparison		1 > 2 > 3,4,5	1,2 > 3,4,5

Notes: SD = Standard deviation; χ^2 = Kruskal–Wallis test value; F = ANOVA test value; SCI = Spinal cord injury; *p < 0.05 indicates statistical significance.

The Immunohistochemical analysis confirmed that ADNP proteins were present in every group of samples. The ADNP protein marker appeared in both neuronal cells and glial cells throughout all experimental groups. The control samples and laminectomy samples maintained their typical ADNP protein patterns. The treatment groups 3, 4 and 5 demonstrated elevated ADNP protein expression levels than the control samples. The staining intensity of ADNP in Group 4 was moderate but Group 5 (pregabalin) had the strongest staining among all treatment groups. The majority of ADNP-positive cells resided in the anterior horn area. The negative control sections remained unstained because they proved the antibodies were specific (Figure 2).

Serum ADNP levels were measured using ELISA. The for Group 2 (laminectomy) were 2.639 ± 0.239 while Group 3 (SCI) recorded 2.606 ± 0.275 and Group 4 control group displayed 3.012 ± 0.084 absorbance units. The absorbance values (methylprednisolone) recorded 2.344 ± 0.685 and Group 5 (pregabalin) recorded 2.739 ± 0.383. The analysis revealed no statistically meaningful variations between the different groups ($F=2.316$, $p=0.085$). The coefficient of variation was highest in the methylprednisolone group (Figure 3, Table 3).

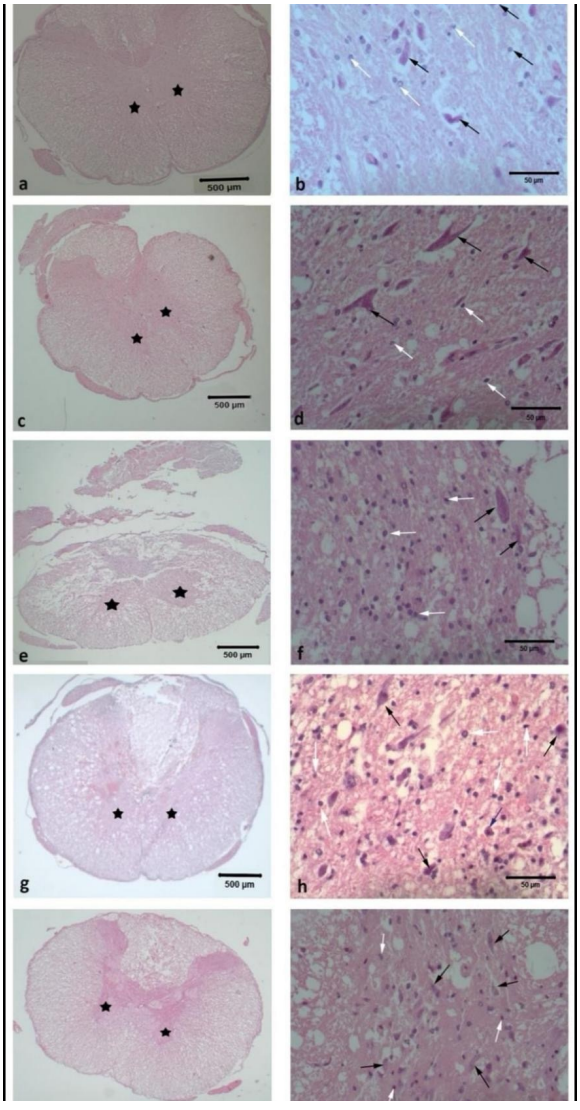

Figure 1. HE staining performed for histological evaluation in all groups. a-b: Control group, c-d: Laminectomy group, e-f: Laminectomy + spinal cord injury group, g-h: Laminectomy + spinal cord injury + methylprednisolone treatment group, i-j: Laminectomy + spinal cord injury + pregabalin group. Spinal cord anterior horn (stars), anterior horn motor neurons (black arrows), glial cells (white arrows). An increase in the number of glial cells is observed in the trauma groups.

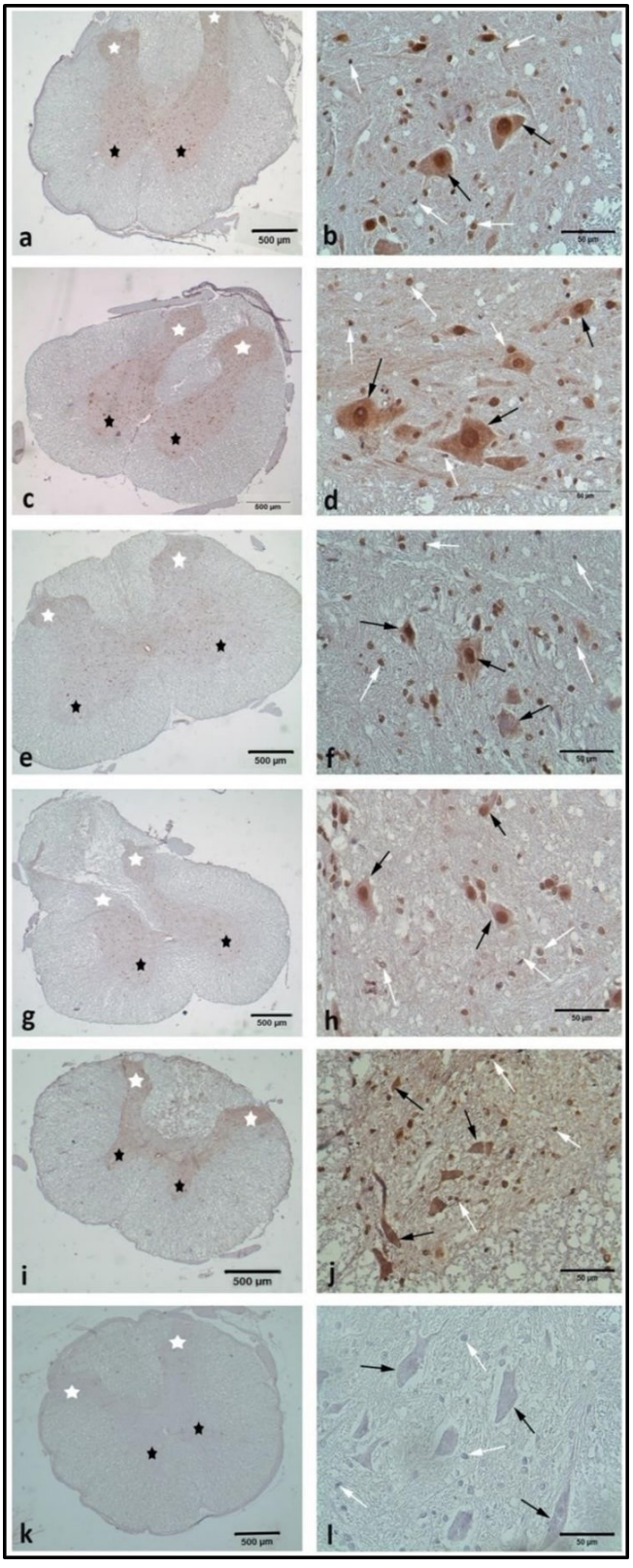

Figure 2. ADNP immunohistochemical staining in all groups. a-b: Control group, c-d: Laminectomy group, e-f: Laminectomy + spinal cord injury, g-h: Laminectomy + spinal cord injury + methylprednisolone treatment group, i-j: Laminectomy + spinal cord injury + pregabalin group, k-l: Negative control staining. Spinal cord anterior horn (black stars) and posterior horn (white stars) neurons and glial cells show ADNP positive reaction. High magnification reveals ADNP positive reaction in anterior horn motor neurons (black arrows) and glial cells (white arrows). No immunoreaction is observed in the negative control staining; only haematoxylin staining is present.

Table 2. Histological Counting Parameters

Groups	n	Neuron Count Mean ± SD	Glial Cell Count Mean ± SD	Neuron/ Total Cells (%) Mean ± SD
Control (1)	110	11.38 ± 3.02	25.48 ± 10.02	32.61 ± 9.34
Laminectomy (2)	73	8.64 ± 2.68	24.82 ± 8.01	27.13 ± 8.31
Laminectomy + Spinal Cord Injury (3)	65	5.06 ± 2.55	35.12 ± 9.49	13.02 ± 6.54
SCI + Methylprednisolone (4)	84	6.80 ± 2.59	26.37 ± 9.60	20.52 ± 7.96
SCI + Pregabalin (5)	40	9.68 ± 3.58	41.15 ± 12.12	21.14 ± 10.35
Statistical Analysis		F = 60.89; p < 0.01*	F = 42.02; p < 0.01*	F = 72.79; p < 0.01*
Post-hoc Comparison		1 > 2,5 > 3,4	5 > 3 > 1,2,4	1 > 2 > 4,5 > 3

Notes: SD = Standard deviation; F = ANOVA test value; *p < 0.01 indicates statistical significance; n = Number of evaluated image fields; Post-hoc comparisons were performed using Sidak's multiple comparison test.

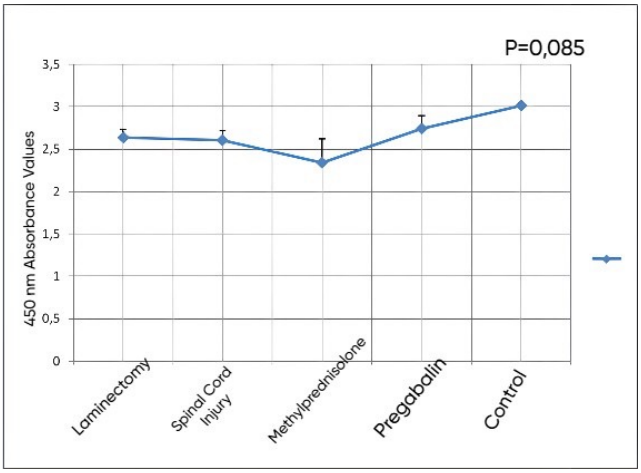

Figure 3. ELISA Graph: Graph created based on the average absorbance values for each group.

Discussion

The research examined pregabalin effects on ADNP gene expression and spinal cord tissue protection following experimental spinal cord damage. The research showed pregabalin treatment maintained neuron numbers while it stimulated glial cell growth and boosted ADNP expression above the injury-only and methylprednisolone groups.

Motor Function Recovery

Our findings on spinal cord injury-induced motor function deficits were consistent with previous literature [13]. The inclined plane test produced equivalent functional deterioration across all trauma groups which validated our injury model [16]. The but the difference failed to achieve statistical significance ($p>0.05$). motor function scores of pregabalin-treated animals were slightly higher than methylprednisolone-treated animals. Bhagwani et al. (2017) demonstrated that pregabalin at 30 mg/kg reduced spasticity through glutamatergic transmission blockage [16]. The limited motor improvement in our study may be attributed to the short 7-day follow-up period, which might be insufficient to detect functional recovery differences.

Histopathological Changes and Glial Response

The pregabalin group maintained its neuronal numbers at 9.68 ± 3.58 compared to the SCI-only group which had 5.06 ± 2.55 neurons while showing substantial glial cell growth (41.15 ± 12.12). The glial cell growth in this study appears to function as a protective mechanism instead of developing into pathological gliosis. Research indicates that astrocytes which react to injury consist of multiple cell types which either help or harm the tissue [17]. The study by Hong et al. (2024) showed that pregabalin treatment leads to the development of anti-inflammatory M2 microglial cells [18]. Our increased glial cell counts may similarly reflect a shift toward neuroprotective glial phenotypes, though phenotypic characterization was not performed in this study.

ADNP Expression and Neuroprotective Mechanisms

The pregabalin-treated animals showed the highest ADNP expression levels among all injury groups. The results indicate that the body activates its natural defense mechanisms to protect the brain. The α2-δ subunit of voltage-gated calcium channels which pregabalin modulates could control ADNP expression through calcium signal transduction pathways [19, 20]. The calcium regulation functions of ADNP together with its role in synaptic plasticity suggest that pregabalin treatment may lead to improved synaptic function [21]. Research using NAP peptide which originates from ADNP showed that this peptide improved functional outcomes in traumatic brain injury models [21,22] which supports our findings about ADNP's protective effects on the brain.

Serum ADNP Levels and Biomarker Potential

The pregabalin group demonstrated elevated serum ADNP levels at 2.739 ± 0.383 but the results failed to reach statistical significance ($p=0.085$). The results might stem from our restricted participant number ($n=8$ per group) or the point at which we took blood samples. The study by Kapitansky et al. (2019) suggested serum ADNP could function as a biomarker for neurodegenerative diseases [19]. The exact pattern of ADNP release into circulation and the relationship between tissue and serum ADNP levels during acute spinal cord injury needs additional research.

Comparison with Methylprednisolone

The methylprednisolone group demonstrated poor neuronal survival and reduced ADNP gene expression when compared to pregabalin treatment. The use of high-dose corticosteroids leads to the reduction of endogenous neuroprotective mechanisms which include neurotrophic factor production [23,24]. The results indicate pregabalin provides superior benefits than conventional steroid treatment because it supports natural protective systems instead of blocking them.

Study Limitations

The study contains multiple restrictions which need to be recognized: 1. The 7-day observation period failed to show how patients would recover functionally in the long term and how their condition would change during the chronic phase 2. The study used basic motor tests for functional assessment but did not perform a complete behavioral evaluation that included BBB score and sensory testing 3. The study used a single pregabalin dose of 50 mg/kg which prevented researchers from studying different dose levels 4. The research failed to study the biological pathways which control ADNP protein expression 5. The study did not perform glial cell identification or inflammatory marker detection 6. The research might have lacked sufficient participants to detect meaningful changes in serum ADNP

concentrations. The study's results become less applicable to other populations because the researchers worked with only a few experimental participants [25].

Future Directions

Research should concentrate on pregabalin dose-finding studies and extended observation periods to study long-term results and should include complete functional tests that measure sensory and autonomic function. Research should focus on studying ADNP signaling pathways at the molecular level and performing glial cell phenotyping to verify protective polarization and testing combination treatments. The study of pregabalin effects on glial scar development and axonal growth during the chronic phase would deliver essential knowledge.

Conclusion

The research demonstrates that pregabalin therapy protects brain cells while increasing ADNP gene expression after spinal cord damage in experimental models. The 7-day observation period showed limited functional enhancement yet the study revealed promising neuroprotective effects through histological and molecular analysis. The research needs to continue with longer observation times and complete functional tests and detailed studies of mechanisms before it can be considered for human use. Scientists should study ADNP as a therapeutic target for spinal cord injury treatment because it shows promise as a mediator of pregabalin's neuroprotective effects.

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