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The Effect of Piracetam Administration on Cerebral Palsy Prevention in Rat Fetuses Born To Pregnant Rats by Determining Bdnf Levels in Brain Tissue

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Abstract

Cerebral palsy is the most common cause of disability in children worldwide, estimated prevalence of 1.5–4 per 1000 children; the higher prevalence in low-resource populations (up to 10 per 1000 children). Brain-derived neurotrophic factor (BDNF) is potent modulator of many neuronal functions that protect the newborn or developing brain from ischemic injury. The expression of GluN3A, which plays a neuroprotective role, is rapidly induced during cerebral ischemia and hypoxia. This study assessed the effect of piracetam administration on BDNF and GluN3A levels in the brain tissue to determine its potential to prevent cerebral palsy. In this experimental study with a post-test-only control group design, a rat model of cerebral palsy was established by injecting pregnant rats with LPS on gestation days 15, 17, and 19; piracetam was administered orally on day 10.5. BDNF and GluN3A protein levels and mRNA expression in the foetal brain tissue of 36 subjects were evaluated with enzyme-linked immunosorbent assay (ELISA) and real-time polymerase chain reaction (RT-PCR). BDNF and GluN3A protein levels in the foetal brain differed significantly between the control and treatment groups ($p < 0.05$). A decrease in the mRNA and protein levels of BDNF and GluN3A was observed in all treatment groups, but the statistical analysis of RT-PCR did not reveal significant differences between the control and treatment groups ($p > 0.05$). These results indicate that piracetam can prevent cerebral palsy in a foetal rat model established via prenatal LPS injection, as assessed by the protein expression of BDNF and GluN3A mRNA.

Keywords: BDNF, Cerebral palsy, GluN3A, piracetam, rats.

Introduction

Cerebral palsy exhibits great diversity in its aetiology and the type and severity of motor disability and related disabilities. Several relatively consistent relationships have been described between its aetiology, pathology, and clinical features, such as sustained neonatal hyperbilirubinaemia, kernicterus, and dyskinetic cerebral palsy. The disease is commonly associated with preterm birth and periventricular leukomalacia (PVL). PVL is the leading cause of cerebral palsy and cognitive deficits

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in preterm infants[1, 2], and the incidence of PVL decreases with gestational age[3]. Glutamatergic synapses are the main excitatory synapses in the brain, especially in the cerebral cortex and hippocampus. Over 80% of synapses in the cortex are glutamatergic[4], and glutamatergic transmission plays a major role in neuronal function in the brain. Imbalances in glutamatergic signalling can lead to several neurodegenerative and psychiatric conditions[5].

Brain-derived neurotrophic factor (BDNF) is a powerful modulator of many neural functions. BDNF has two types that work in different ways. The first type, mature BDNF, is essential for protecting the newborn or developing brain from ischaemic injury. The second type is pro-BDNF, which must be converted back to the mature form through high-frequency neural activity. Pro-BDNF levels are highest during the perinatal period and then decline with age, although the pro-form remains detectable in adulthood. These data suggest that the brains of newborns and infants are more susceptible to ischaemic stroke due to low-frequency neural activity and a lack of adequate amounts of mature BDNF in the central nervous system (CNS)[6].

GluN3A is an isoform of GluN3B, both of which are subunits of GluN3, the third member of the N-methyl-D-aspartate receptor (NMDAR) subunits. GluN3 exhibits inhibitory effects on NMDAR activity. GluN3A is predominantly expressed during early development, although its expression in certain populations of neurons persists in adults. GluN3A affects dendrite density, synapse maturation, memory consolidation, and cell survival. The expression of GluN3A, which is neuroprotective, is rapidly induced during cerebral ischaemia and hypoxia [7].

In recent years, intrauterine interventions such as foetoscopy (minimally invasive foetal surgery) and open foetal surgery have increased, and artificial reproductive techniques that increase the rate of multiple pregnancies (e.g. in vitro fertilization) have become more common; these are risk factors for preterm birth, and no effective therapies are yet available to prevent cerebral palsy or reduce its severity in preterm infants[8]. However, many studies are being conducted in animal models to evaluate new treatments for humans and elucidate the pathological mechanisms involved in disease progression[9, 10].

Preterm birth is common, and one of its complications is cerebral palsy; thus, interventions should be initiated as early as possible in the foetu[11]. Therefore, this study examined the impact of piracetam administration on the mRNA expression of BDNF and GLUN3A in the foetal brain in a rat model of cerebral palsy established via prenatal LPS injection in pregnant rats. The results of this study provide a basis for considering this treatment for preterm infants.

Materials and Methods

Healthy Wistar rats (*Rattus norvegicus*) of childbearing age (10 males weighing 290–300 g and 20 females weighing 240–250 g) were housed in a standardised animal centre (at 23 ± 2 °C and 55% humidity) with free access to food and water. A diurnal rhythm of 12 hours of light and 12 hours of dark was maintained throughout the study. After 1 week of adaptive feeding, the rats were caged together with a male-to-female ratio of 1:2, and vaginal smear examinations began the next day. Day 1 of gestation was recorded when the sperm plug was found. A total of 63 pregnant rats were randomly divided into two groups: a cerebral palsy model group, in which rats were injected intracervically with 1 mg/kg body weight of lipopolysaccharide (LPS) suspended in saline at 15, 17, and 19 days of gestation (G20), and a control group, in which rats were injected with the same volume of saline[12]. Piracetam was orally administered to the treatment groups on day 10.5 at doses of 50, 100, 150, and 200 mg in an attempt to prevent cerebral palsy in the offspring; on day 19, several hours after the final injection, the foetuses were born prematurely.

Statistical Analysis

SPSS version 20.0 was used to analyze the data. The normality of each variable was assessed with the Shapiro–Wilk test. The distribution of the sample variables was considered normal ($p > 0.05$), and the data were thus evaluated with one-way analysis of variance (ANOVA). The statistical significance of the differences in variables between groups ($p < 0.05$) was compared using post hoc least significant difference (LSD) analysis and a non-normal distribution ($p < 0.05$). The Kruskal–Wallis test was used, along with Mann–Whitney analysis.

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Research Sample

The minimum sample size was calculated with the G*Power application. To calculate the sample size for one-way ANOVA, data on the effect size (f), type I error rate (α), power, and number of treatment groups are needed. The effect size describes the difference in population effects obtained from previous studies, or data from previous studies can be converted into the effect size needed for this formula. In the absence of effect size data from previous studies, a standardised effect size can be used, with an effect size of 0.20 for small effect differences in the population, 0.50 for medium effect differences in the population, and 0.80 for large effect differences in the population[11]. Assuming a moderate effect difference in the population, using an effect size (f) of 0.50, a type I error rate (α) of 0.5, and a power of 0.80, the minimum sample size for four treatment groups was 35 subjects, or 5 subjects per group[13].

Examination of molecular protein

BDNF and GluN3A levels were measured by first isolating the brain tissue of the foetuses. Subsequently, the brain tissue was washed in normal saline, fixed in 10% neutral buffered formalin solution, and frozen using liquid nitrogen in a round microbottle vessel[14].

Examination procedure of real-time polymerase chain reaction

BDNF and GluN3A mRNA expression was measured by isolating the brain tissue of the foetuses. Next, the brain tissue was washed in normal saline, fixed in 10% neutral buffered formalin solution, and frozen using liquid nitrogen in a round microbottle vessel. The most common method for mRNA analysis was in situ hybridization and quantitative real-time polymerase chain reaction (RT-qPCR).

Results

Examination of BDNF protein levels in brain tissue of foetuses with periventricular leukomalacia or cerebral palsy

The results revealed significant differences in BDNF levels between the brain tissue of foetuses with periventricular leukomalacia or cerebral palsy in the control group and the treatment group ($p < 0.05$). Piracetam was orally administered to pregnant rats (which were injected with LPS to induce periventricular leukomalacia or cerebral palsy in the foetuses) at doses of 50, 100, 150, and 200 mg/day.

The LSD one-way ANOVA post hoc test revealed a significant difference in BDNF levels (pg/mL) in the brain tissue of the foetal rats with periventricular leukomalacia or cerebral palsy induced by LPS injection between the control group (K2) and treatment groups (P2, P3) ($p < 0.05$, Table 1.

Table 1. BDNF levels (pg/ml) in brain tissue of rat fetuses born to pregnant rats with periventricular leukomalacia or cerebral palsy models.

Groups	Mean ±SD (pg/ml)	p value	Post Hoc					
			K2	K3	P1	P2	P3	P4
K1	341,737±26,914		0.446	1	0.997	0.722	0.876	0.998
K2	503,579±7,627			0.418	0.178	0.024**	0.048**	0.571
K3	363,813±7,753	0.03*			0.997	0.893	0.289	0.479
P1	337,789±22,636					0.959	1	0.289
P2	294,368±5,642						0.959	0.994
P3	216,737±4,971							1
P4	241,737±3,924							

Description: data presented as mean±SD
K1= without injection LPS, K2 =injection LPS, K3= injection aqua (placebo)
P1 =piracetam 50 mg, P2 =piracetam 100 mg, P3 = piracetam 150 mg, P4 = piracetam 200 mg
*p <0.05, *One Way Anova test*
**$p<0.05$, *Post Hoc LSD test*

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Examination of BDNF mRNA expression in brain tissue of foetuses with periventricular leukomalacia or cerebral palsy

The RT-PCR results of BDNF mRNA expression were analysed by one-way ANOVA, which did not reveal any statistically significant differences between the control group and the treatment group ($p > 0.05$), as shown in the Fig. 1.

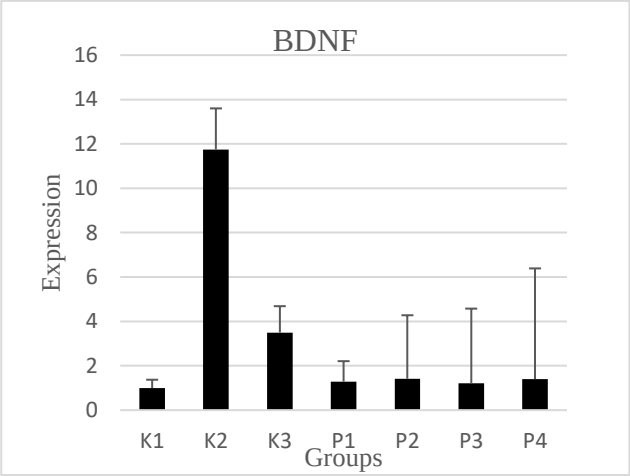

Figure 1. Real time PCR of BDNF mRNA (pg/ml) in fetal brain tissue in pregnant rats model of periventricular leukomalacia or cerebral palsy group, p>0.05.

Examination of GluN3A protein and mRNA levels (pg/mL) in brain tissue of foetal rats with periventricular leukomalacia or cerebral palsy

GluN3A levels (pg/mL) were significantly different between the control group and the treatment group ($p < 0.05$) according to the Kruskal–Wallis test with Mann–Whitney post hoc analysis. We found significant differences between the normal group (K1) and the control groups (K2, K3), along with significant differences between all treatment groups (P1, P2, P3, and P4; $p < 0.05$, Table 2.

Table 2. GluN3A protein and mRNA levels (pg/ml) in foetal brain tissue of pregnant rats with periventricular leukomalacia or cerebral palsy models

Groups	Median (min-max) (pg/ml)	p value	Post Hoc K2	K3	P1	P2	P3	P4
K1	25.1 (13.8-63.8)		0.024**	0.031**	0.011**	0.003**	0.001**	0.001**
K2	59.2 (26.9-89)			0.666	0.666	0.863	0.222	0.297
K3	34.7 (16.7-47.5)				0.605	1.000	0.190	0.222
P1	30.5(9.6-43.9)	0.023*				0.931	0.258	0.258
P2	42.6 (10.2-59.3)						0.258	0.222
P3	36.9 (22.8-102.6)							0.931
P4	39.4 (31-59.3)							

Description: data presented median (minimum –maximum)
K1= without LPS injection, K2 =LPS injection, K3= aqua injection (placebo)
P1=piracetam 50 mg, P2=piracetam 100 mg, P3=piracetam 150 mg, P4=piracetam 200 mg
**p* <0.05, *Kruskall - Walliis*
***P<0.05, post hoc Man Witney*
p>0.05, One way Anova test

One-way ANOVA did not reveal significant differences between groups ($p > 0.05$), as shown below.

Fig. 2.

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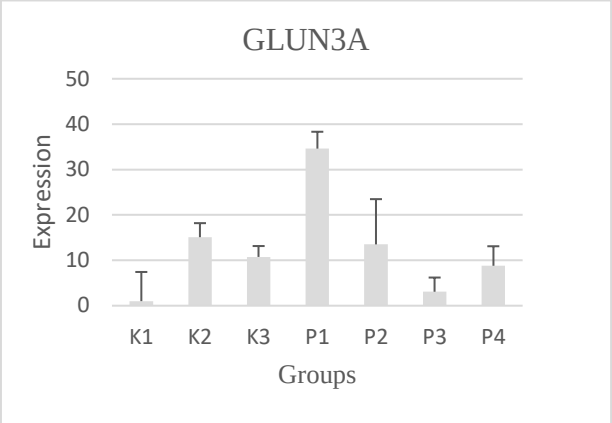

Figure.2. Real Time PCR of GluN3A mRNA (pg/ml) in foetal brain tissue in pregnant rats periventricular leukomalacia or cerebral palsy models in control and treatment group

Discussion

This study examined the effect of piracetam in the prevention of cerebral palsy in foetal rats with prenatal induction of periventricular leukomalacia or cerebral palsy. The cerebral palsy model was established via LPS injection at a dose of 1 mg/kg body weight on gestation days 15, 17, and 19; the pregnancies were terminated on day 19, several hours after the final LPS injection8. Oral administration of piracetam began in the treatment group on day 10.5[15] The use of diagnostics during pregnancy can lead to cerebral palsy in foetuses; therefore, piracetam was administered to prevent cerebral palsy in foetal rats exposed to prenatal LPS injection[16].

LPS induces periventricular leukomalacia or cerebral palsy in foetuses when administered to pregnant rats; this research was carried out by previous researchers[17], who utilized intrauterine administration of LPS. In this study, the foetuses from pregnant rats injected with LPS had significantly different BDNF levels in their brain cells compared with foetuses in the control group ($p < 0.05$). The control group exposed to prenatal LPS (K2) exhibited higher levels of BDNF in the brain cells than the groups without LPS exposure (K1, K3). The increase in BDNF levels was due to the induction by LPS[17]. These results align with those of previous research, which reported that BDNF concentrations were high during the first week after trauma[18].

In this study, the oral administration of piracetam in pregnant rats injected with LPS reduced BDNF levels in the foetuses of all piracetam dosage groups (P1, P2, P3, and P4). Previous research revealed an increase in BDNF mRNA expression in the lateral ipsi hippocampus and cortex 1–2 days after clinical traumatic brain injury[19].A different study reported a decrease in BDNF levels in patients with cerebral palsy[20], and other studies have indicated that BDNF can be used as a biomarker for cerebral palsy[21, 22].

This study revealed higher GluN3A levels in the LPS-exposed group compared with those in the group not exposed to LPS and the placebo group. Oral piracetam administration was associated with a decrease in GluN3A levels at all doses compared with the control group that received LPS injection. GluN3A plays an important role in the CNS by delaying synapse maturation. The reactivation of GluN3A expression at inappropriate ages may underlie the maladaptive synaptic rearrangements observed in addiction, neurodegenerative diseases, and other major brain disorders[23, 24]. In this study, 50 mg of piracetam was considered the best dose because the GluN3A mRNA and protein levels suggested that using this dose does not inhibit the ability of GluN3A mRNA to produce GluN3A protein.

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Conclusion

Oral piracetam can be used to prevent cerebral palsy in rat fetuses from pregnant rats in which LPS is used to establish a model with cerebral palsy. We observed a significant decrease in BDNF and GluN3A protein expression and a decrease in BDNF and GluNa3A mRNA expression in the foetal brain tissue. After clinical trials, this treatment can be recommended for administration during pregnancies with a risk of premature labour/birth.

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Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for republication, which is attached to the manuscript.
- The authors have signed an animal welfare statement.
- Ethical Clearance: The project was approved by the local ethical committee at Universitas Sumatera Utara.
- No human studies are present in the manuscript.
- No potentially identified images or data are present in the manuscript.
- Ethic Statement: All animal experiments complied with ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. The research protocol applied in this research has been approved by The Research Ethics Committee at Medical Faculty, Universitas Sumatera Utara (approval No. 204/KEP/USU/2022).

Authors' Contribution Statement

D.A, S.N.L, I.L.F, K.P.S and A.S contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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تأثير إدارة البيراسيتام على الوقاية من الشلل الدماغي في أجنة الفئران المولودة للفئران الحوامل عن طريق تحديد مستويات Bdnf في أنسجة المخ

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الخلاصة

الشلل الدماغي هو السبب الأكثر شيوعًا للإعاقة لدى الأطفال في جميع أنحاء العالم، ويقدر معدل انتشاره بـ 1.5-4 لكل 1000 طفل؛ ارتفاع معدل الانتشار بين السكان ذوي الموارد المنخفضة (ما يصل إلى 10 لكل 1000 طفل). عامل التغذية العصبية المشتق من الدماغ (**BDNF)** هو مُعدِّل قوي للعديد من الوظائف العصبية التي تحمي الوليد أو الدماغ النامي من الإصابة الإقفارية. يتم تحفيز التعبير عن **GluN3A**، الذي يلعب دورًا وقائيًا للأعصاب، بسرعة أثناء نقص تروية الدماغ ونقص الأكسجة. قيمت هذه الدراسة تأثير إعطاء البيراسيتام على مستويات **BDNF** و**GluN3A** في أنسجة المخ لتحديد قدرته على الوقاية من الشلل الدماغي. في هذه الدراسة التجريبية مع تصميم مجموعة مراقبة بعد الاختبار فقط، تم إنشاء نموذج فأر للشلل الدماغي عن طريق حقن الفئران الحوامل بـ **LPS** في أيام الحمل 15 و17 و19؛ تم إعطاء البيراسيتام عن طريق الفم في اليوم 10.5. تم تقييم مستويات البروتين **BDNF** و**GluN3A** وتعبير **mRNA** في أنسجة المخ الجنينية لـ 36 شخصًا باستخدام مقايسة الامتصاص المناعي المرتبط بالإنزيم (**ELISA)**وتفاعل البوليميراز المتسلسل في الوقت الحقيقي (**RT-PCR).** اختلفت مستويات البروتين **BDNF** و**GluN3A** في دماغ الجنين بشكل كبير بين مجموعتي التحكم والعلاج (**P <0.05).** ولوحظ انخفاض في مستويات الرنا المرسال ومستويات البروتين لـ **BDNF** و**GluN3A** في جميع مجموعات العلاج، لكن التحليل الإحصائي لـ **RT-PCR** لم يكشف عن فروق ذات دلالة إحصائية بين مجموعتي المراقبة والعلاج (**p > 0.05).** تشير هذه النتائج إلى أن البيراسيتام يمكن أن يمنع الشلل الدماغي في نموذج الفئران الجنينية الذي تم إنشاؤه عن طريق حقن **LPS** قبل الولادة، كما تم تقييمه من خلال التعبير البروتيني لـ **BDNF** و**GluN3A mRNA.**

الكلمات المفتاحية: BDNF، الشلل الدماغي، GluN3A، بيراسيتام، الفئران.