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Original Article

Impact of Human Chorionic Gonadotropin on Pentylenetetrazol-Induced Seizure Activities in Mice: Modulation of miR-181a Expression as a Potential Neuroprotective Mechanism

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Abstract

Introduction: Epilepsy affects millions of people globally, with 30% of patients exhibiting drug resistance, necessitating novel therapies. Human chorionic gonadotropin (hCG), known for neuroprotective effects, has been underexplored in epilepsy despite its role in neuronal survival. Therefore, this study aimed to evaluate hCG's anticonvulsant potential in a pentylenetetrazole (PTZ)-induced seizure model in male mice and to assess its impact on the hippocampal gene expression of microRNA-181a (miR-181a), brain-derived neurotrophic factor (BDNF, Bcl-2-associated X protein (Bax), and B-cell lymphoma 2 (Bcl-2).

Methods: Male mice (n = 7 per group) received hCG (1500 IU/kg, intraperitoneal) or saline for 5 days, followed by PTZ (80 mg/kg) to induce seizures. Seizure latency was recorded, and hippocampal gene expression was analyzed via real-time polymerase chain reaction.

Results: hCG pretreatment significantly delayed seizure onset compared to the PTZ-only group ($P < 0.001$). No significant changes were observed in miR-181a, BDNF, or Bcl-2 expression ($P > 0.05$), while Bax was elevated in PTZ and PTZ+hCG groups ($P < 0.01$ and $P < 0.001$, respectively).

Conclusion: hCG's anticonvulsant effect, likely mediated by N-methyl-D-aspartate receptor inhibition, highlights its therapeutic potential independent of apoptotic or neurotrophic gene modulation. In contrast to the findings of chronic epilepsy models, where miR-181a and BDNF alterations are prominent, our results demonstrated a different underlying mechanism. Limitations included the acute model's limited generalizability and lack of protein-level validation. Accordingly, future studies should explore chronic models and alternative mechanisms, such as oxidative stress pathways. Overall, hCG's established safety supports its potential as an adjunctive therapy for epilepsy, addressing drug resistance challenges.

Keywords: Epilepsy, Human chorionic gonadotropin, Pentylenetetrazole, miR-181a, Neuroprotection

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Introduction

Epilepsy is a chronic neurological condition that is marked by recurrent abnormal electrical activities in the brain, impacting approximately 65 million people worldwide. This multifaceted disorder involves widespread alterations in brain function at molecular, cellular, and network levels. In addition, it may arise from genetic abnormalities or be triggered by epileptogenic events, including traumatic brain injury, brain infections, stroke, or status epilepticus (1). Human chorionic gonadotropin (hCG) is a dimeric glycoprotein hormone that interacts with the G-protein-coupled receptor, commonly referred to as the luteinizing hormone (LH)/hCG receptor (2). The LH/hCG receptor plays an essential role in brain development, neuronal differentiation, and function. When exposed to highly purified hCG, cultured rat neurons exhibit a dose-dependent response, which is characterized by enhanced neurite outgrowth, increased total cellular protein, and reduced apoptosis (3). Growing clinical and experimental data suggest that steroid hormones modulate neuronal excitability, thereby impacting brain functions (4). The synthesis of steroid hormones, whether in peripheral tissues (gonads or adrenals) or centrally (glial cells), is regulated by the periodic release of hCG. Neurosteroids significantly influence ictal activity, potentially through their effects on gamma-aminobutyric acid (GABA) and/or glutamate systems (5). Micro ribonucleic acids (miRNAs) are short non-coding RNA molecules that post-transcriptionally control gene expression through messenger RNA (mRNA) degradation or translational repression. The miR-181 and miR-125 families display strong evolutionary conservation across humans. The miR-181 family includes four distinct members

(miR-181a, miR-181b, miR-181c, and miR-181d), and abnormal expression levels of these miRNAs have been associated with multiple neurological conditions (6). Moreover, miR-181a is prominently expressed in the hippocampus, which is a critical brain region for various types of memory formation. It suppresses hippocampal neuronal development and synaptic function by negatively regulating the expression of cyclic adenosine monophosphate response element-binding protein 1 (CREB) or the glutamate receptor subunit A2, respectively (7). The *Bcl-2* gene family comprises both anti-apoptotic and pro-apoptotic genes that control apoptosis by modulating mitochondrial membrane permeability. Research indicates that the Bcl-2/Bax ratio is directly related to apoptosis regulation, where a decreased ratio correlates with increased apoptosis (8). Repeated epileptic seizures can trigger neuronal apoptosis, leading to a reduction in cell numbers. This cell loss can recognize neuronal synapses, forming aberrant synaptic circuits that contribute to the recurrence of epilepsy (9). This study aims to investigate the anticonvulsant effects of hCG in a pentylenetetrazole (PTZ)-induced seizure model in male mice. Additionally, it evaluates whether hCG pretreatment delays seizure onset and modulates hippocampal expression of miR-181a, BDNF, Bax, and Bcl-2. Ultimately, the research seeks to elucidate hCG's neuroprotective mechanisms and its potential as a novel therapy for epilepsy.

Materials and Methods

Animals

The research received ethical clearance from the Institutional Animal Care and Use Committee at Shahrekord University of Medical Sciences. Male mice were housed in groups of 3–4 per standard cage, maintained on a 12-hour light/dark schedule with ad libitum access to food and water. In addition, all experimental protocols complied with applicable ethical standards and regulations. Furthermore, the animals were kept under controlled conditions (temperature of 25 ± 1°C and humidity of 50 ± 5%) with constant access to standard chow and drinking water.

Pentylenetetrazole-Induced Seizures

PTZ (60 mg/mL) was administered via tail vein infusion in freely moving mice at a steady rate of 0.3 mL/min using a 30-gauge dental needle connected to a Hamilton microsyringe through polyethylene tubing. Further, the endpoint was defined as the onset of generalized clonus, characterized by the clonic movements of all four limbs and a temporary loss of the righting reflex. Moreover, the seizure threshold was determined by measuring the time from PTZ injection to seizure onset.

The animals were allocated to the control, PTZ, and hCG+PTZ groups receiving saline (0.5 mL, orally; n = 7), PTZ (60 mg/mL, via tail vein infusion; n = 7), and hCG (1500 IU/kg, intraperitoneally for 5 days; n = 7) prior to PTZ infusion, respectively.

After the 5-day protocol, mice were euthanized by the intravenous injection of 1% sodium thiopental (30 mg/kg over 30 seconds), followed by cervical dislocation and decapitation. Then, brains were rapidly removed and washed in ice-cold 0.9% saline, and hippocampi were dissected for subsequent biochemical assays.

Measurement of miR-181a, Bax, Bcl-2, and BDNF Gene Expression

In this study, real-time quantitative polymerase chain reaction (qPCR) was employed to analyze the expression of target genes in brain tissue. Total RNA was extracted from tissue samples and purified using commercial kits. Subsequently, complementary DNA was synthesized using reverse transcriptase. RT-PCRs were performed using SYBR Green and gene-specific primers under standardized thermal cycling conditions (denaturation: 95°C, annealing: 60°C, extension: 72°C) on an Applied Biosystems instrument. Finally, data were normalized via the ΔΔCt method, with gene expression calculated relative to internal controls (glyceraldehyde-3-phosphate dehydrogenase or beta-actin). Each sample was analyzed in triplicate, and the results were expressed as mean ± scanning electron microscopy (10).

Data Analysis

Statistical analyses were conducted in GraphPad Prism 6 using a one-way analysis of variance (ANOVA), followed by Tukey's post-hoc test; data are reported as means ± scanning electron microscopy, with $P < 0.05$ considered statistically significant. Seizure latency between the PTZ-only and PTZ+hCG groups was compared via an independent-samples t-test.

Results

Effect of Human Chorionic Gonadotropin on the Onset of Seizure

The seizure latency in male mice subjected to PTZ-induced kindling and pretreated with hCG at a dose of 1500 IU/kg intraperitoneally for 5 days was significantly prolonged compared to the group treated with PTZ alone (60 mg/kg) ($P = 0.002$, Figure 1).

Hippocampal miR-181a Gene Expression

Our findings indicated that hippocampal *miR-181a* gene expression in PTZ-kindled rats did not significantly differ from that in the control group receiving normal saline ($P > 0.05$). Similarly, miR-181a expression in the hippocampus of PTZ-kindled mice pretreated with hCG (1500 IU/kg) showed no significant difference compared to the PTZ-only group ($P = 0.23$, Figure 2).

Hippocampal BDNF, Bcl-2, and Bax Gene Expression

Hippocampal BDNF and Bcl-2 mRNA levels in PTZ-kindled rats demonstrated no significant difference from saline-treated controls ($P = 0.20$ and $P = 0.031$, respectively). Likewise, hCG pretreatment (1500 IU/kg) in PTZ-kindled mice did not alter hippocampal

BDNF or Bcl-2 expression compared with the PTZ-only group ($P=0.33$). In contrast, Bax mRNA was markedly upregulated in the hippocampus of PTZ-kindled mice versus saline controls ($P=0.001$), with even greater elevations in the hCG + PTZ group ($P=0.000$). Related data are displayed in Figure 3A-C).

Discussion

This study assessed whether hCG could confer anticonvulsant protection in male mice that were subjected to PTZ-induced seizures and to quantify concomitant changes in the hippocampal expression of miR-181a, BDNF, Bax, and Bcl-2. It was hypothesized that the neuroprotective actions of hCG would delay seizure onset and correct the expression profiles of genes involved in apoptosis, neuroinflammation, and neurotrophic support, which are all known to be relevant to epilepsy. Our data partially corroborate these predictions: exposure to hCG (1500 IU/kg, i.p. for 5 days) markedly prolonged the interval to the first seizure compared to untreated mice receiving PTZ ($P<0.001$), confirming anticonvulsant

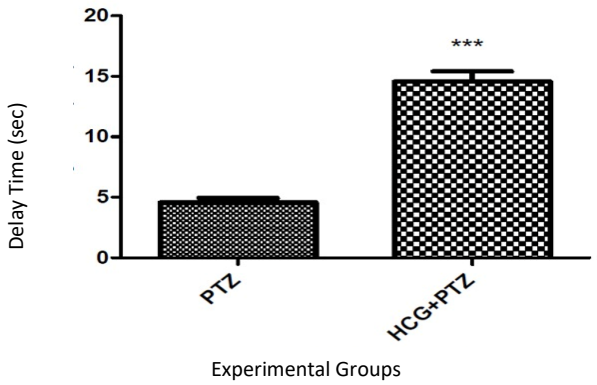

Figure 1. Effect of HCG on the Onset of Seizures
Note. HCG: Human chorionic gonadotropin; PTZ: Pentylenetetrazole. ***$P<0.001$ compared to the PTZ group

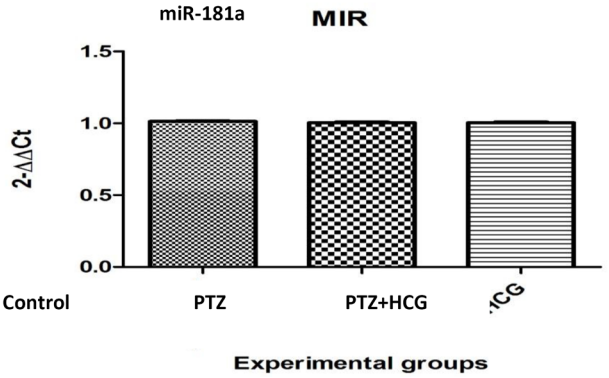

Figure 2. Comparison of *miR-181a* Gene Expression in the Hippocampus of the Experimental Groups
Note. HCG: Human chorionic gonadotropin; PTZ: Pentylenetetrazole; ANOVA: Analysis of variance. Tukey's post-hoc test was performed following one-way ANOVA to identify specific pairwise differences between the groups. The results were deemed statistically significant when $P<0.05$

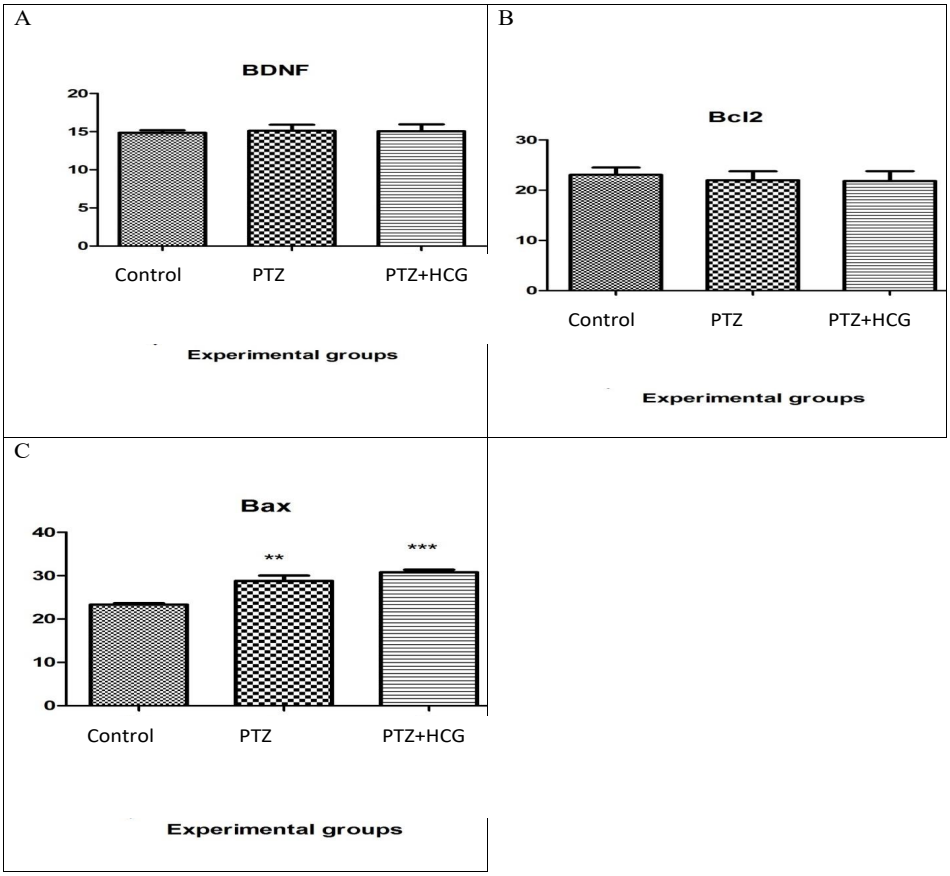

Figure 3A-B-C. Hippocampal *BDNF*, *Bcl-2*, and *Bax* Gene Expression
Note. HCG: Human chorionic gonadotropin; PTZ: Pentylenetetrazole; ANOVA: Analysis of variance. *** $P<0.001$ and ** $P<0.01$. Tukey's post-hoc test was conducted after the one-way ANOVA to determine specific pairwise differences between the groups. The results were statistically significant at $P<0.05$

relevance. Nonetheless, expression analyses revealed that miR-181a, BDNF, and Bcl-2 levels in the hippocampus did not exhibit statistically meaningful variations across the experimental cohorts. Contrarily, Bax levels were significantly higher in the PTZ and PTZ+hCG groups compared with controls ($P<0.01$ and $P<0.001$, respectively). This study utilized male mice to eliminate estrous cycle variability. However, gender differences in epilepsy susceptibility and hormone responses necessitate female studies (11). hCG's LH receptor agonism may differentially affect females via ovarian steroid modulation. Collectively, these results suggest that hCG's seizure-mitigating effect does not engage the evaluated transcriptional pathways; such protection may instead arise via alternate mechanisms, including the restraint of aberrant excitatory activity or the attenuation of oxidative stress. Our finding regarding prolonged seizure latency following hCG treatment is consistent with previous data, supporting its neuroprotective function in diverse neuropathological models. For instance, Movsas et al found that hCG administration prior to insult effectively curtailed neurodegeneration in a hypoxic-ischemic paradigm involving neonatal rats, an effect that is partly attributed to diminished excitotoxicity via the blockade of N-methyl-D-aspartate (NMDA) receptor-mediated pathways (12). Our results align with the literature, indicating that PTZ seizures are linked to increased glutamatergic activities through NMDA receptor pathways. The progesterone-hCG delay in the appearance of seizures is explained by a comparable attenuation of that excitatory drive (12). Similarly, Babahajian et al reported the efficacy of hCG in reducing hippocampal neuronal damage and apoptosis following ischemia-reperfusion injuries, thereby justifying its broader neuroprotective application (13). This study, however, extends such research by being the first to document hCG's anticonvulsant action in an acute seizure model, bridging a meaningful literature gap in which hCG has not been adequately studied in epilepsy despite having proven applications in brain development and neuronal protection (14) and in contrast to miR-181a upregulation observed in the models of chronic epilepsy. For example, Lei et al demonstrated elevated miR-181a levels and associated cognitive dysfunction in PTZ-kindled rats after repeated administration (14). Our failure to alter miR-181a levels could be a consequence of the acute, single-dose PTZ model. This discrepancy emphasizes the model's sensitivity to chronicity, as repeated PTZ exposures in the study by Kong et al provoked miR-181a-mediated neuroinflammation and apoptosis that were absent in this study (9).

The unchanged profiles of BDNF and Bcl-2, along with the heightened Bax, further highlight the value of this study. The role of BDNF in epilepsy is opposite: while reduced levels have been correlated with the intensity of seizures in the human and animal models of chronic diseases (15), acute PTZ models have yielded conflicting results, with some finding no change or even elevations (16). Our finding concerning unaltered BDNF levels confirmed that hCG does not have anticonvulsant actions through neurotrophic potentiation in this acute paradigm, in contrast to chronic kindling models, where anticonvulsant pretreatment blocks BDNF downregulation (17). The pro-apoptotic pattern of increased Bax without concomitant Bcl-2 alterations is consonant with apoptosis induction in seizure models (18). However, the finding that hCG cannot reverse this process suggests that its protective actions bypass the regulation of apoptotic genes, possibly tipping the balance toward anti-excitotoxic mechanisms. Moreover, these results add to the literature by questioning the assumption that neuroprotective drugs act equally on apoptosis and miRNA networks and by addressing a gap by assessing hCG's molecular effects on epilepsy-related genes.

In practice, these results have some implications for the treatment of epilepsy, where 30% of patients are drug-resistant and experience side effects from conventional therapies (11). hCG's safety record as an anticonvulsant, with proven safety in reproductive medicine, renders it a prime candidate for repurposing, possibly as a new adjunct therapy that targets excitotoxicity without interfering with crucial gene expression underpinning long-term neuroplasticity. By demonstrating efficacy in an acute model, this research could address knowledge gaps in understanding hCG's mechanisms in the central nervous system, including its ability to cross the blood-brain barrier and act on neuronal receptors (19), thereby informing targeted delivery strategies.

Despite these insights, constraints must be acknowledged as well. This study used a single-dose PTZ model, which may not fully replicate chronic epilepsy, thereby limiting generalizability to human temporal lobe epilepsy, where recurrent seizures foster progressive gene dysregulation (20). Furthermore, our study included a small sample size (n = 10 per group) and exclusively used male mice, which are potential sources of bias in studies of gender differences in hormone responses and epilepsy susceptibility. In addition, gene expression was quantified solely by RT-PCR without validation at the protein level or by functional assays, which can influence conclusions on Bax's role. Moreover, behavioral testing was confined to seizure latency with no cognition or long-term outcomes, and the 5-day hCG paradigm was considered, which might not be an ideal dosing strategy for maximal responses.

Hence, follow-up experiments should employ chronic kindling paradigms to determine the long-term efficacy and gene modulation of hCG. Further, the evaluation of alternative mechanisms, such as lowering oxidative stress via nuclear factor erythroid 2-related factor 2 (Nrf2) pathways or enhancing GABAergic transmission, might resolve the mechanism underlying hCG's anticonvulsant action. Dose-response, gender differences, and combination treatments with standard antiepileptics would enhance translational potential. Finally, the investigation of miR-181a antagonists in combination with

hCG might reveal synergistic actions in chronic models. This acute study captures immediate anticonvulsant effects but cannot assess adaptive responses or tolerance that develop over weeks, which are critical for chronic therapy evaluations (21). Long-term behavioral and molecular monitoring is required accordingly.

Beyond NMDA inhibition, hCG may attenuate oxidative stress by activating the Nrf2 pathway, as demonstrated in ischemia models (22). Additionally, hCG-induced neurosteroid synthesis can enhance GABAergic inhibition (23). These mechanisms warrant investigation through Nrf2/HO-1 expression analysis and GABA/glutamate quantification.

Study Limitations

A key limitation of this study was the assessment of gene expression solely at the mRNA level without protein validation. While qPCR provides reliable transcriptional data, mRNA levels do not always correlate with protein expression due to post-transcriptional regulation (24). Future studies employing Western blotting or immunohistochemistry for BDNF, Bax, Bcl-2, and miR-181a targets (e.g., glutamate receptor subunit A2) are essential to confirm functional pathway involvement. Although the single-dose PTZ model employed in out study captures acute excitotoxicity, it may not perfectly recapitulate chronic epilepsy pathophysiology characterized by progressive neuronal loss and network reorganization (25). The acute nature of this model likely explains the absence of miR-181a and BDNF alterations, which are typically reported in chronic kindling paradigms. Thus, chronic PTZ or pilocarpine models are required to assess hCG's long-term disease-modifying potential.

Conclusion

Overall, our findings demonstrated that hCG pretreatment decidedly delays PTZ-induced seizure onset in mice, validating its anticonvulsant activity for the first time. However, these effects become apparent without modifying the hippocampal expression of miR-181a, BDNF, and Bcl-2, with elevated Bax in seizure groups, suggesting insensitivity to these apoptotic and neurotrophic pathways. These results indicated the potential of hCG as a neuroprotective therapy for epilepsy, contributing to the literature by expanding the therapeutic options beyond conventional antiepileptics to address some challenges, such as drug resistance and side effects. By elucidating hCG's neurological functions, this study highlights its potential for repurposing reproductive hormones for central nervous system ailments and extends these implications to the management of excitotoxicity-driven diseases. Ultimately, hCG's safety profile and efficacy in acute models portend clinical investigation, with potential to optimize treatment outcomes in epilepsy patients by novel mechanism-based therapies.

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Competing Interests

The authors declare no conflicts of interest.

Ethical Approval

This study was conducted in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments, or with comparable ethical standards. The study protocol was reviewed and approved by the Ethics Committee of Shahrekord University of Medical Sciences (approval code: IR.SKUMS.REC.1399.222).

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