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Research Article

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The Influence of Dexamethasone on Apoptotic Genes Expression Changes in Rabies Virus-Infected Mouse Brain Tissue

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Abstract

Rabies is a severe public health issue, particularly in areas with limited vaccination rates. Despite significant progress in comprehending the illness and creating preventative methods, rabies poses a significant public health problem. Glucocorticoids like dexamethasone effectively reduce inflammation and immunomodulation, but their effects on viral infections, with specific reference to the central nervous system (CNS), are complex and unclear. This study focuses on the apoptosis of brain cells in NMRI (Naval Medical Research Institute) mice infected with a viral infection. Infected mice were randomly assigned to four groups (n=10 per group): a control group, a negative control group treated with dexamethasone, an untreated positive control group containing viral components, and a test group expressing viral components and treated with dexamethasone. FAT results showed that the virus components were present in the brain tissue of NMRI mice; intense positive staining was observed. AKT, BAX, and BCL2 expression were significantly lowered in rat brain tissue compared to untreated mice ($p<0.05$). This study demonstrates the significant change effected by dexamethasone in the pathway of brain cell death in mouse brain tissue. The findings of this study could have significant implications for the risk-benefit ratio of dexamethasone therapy in viral CNS infections and guide possibly more effective and safer treatment strategies in such conditions.

Keywords: Rabies; Dexamethasone; Apoptosis; Central nervous system; Viral infection; Immunomodulation.

1. Introduction

Rabies is a lethal viral infection that affects the central nervous system of mammals, including humans. The rabies virus belongs to the *Rhabdoviridae* family. It is primarily transmitted through the bite of an infected animal, with dogs being the most common source of human rabies infections globally. Upon entry into the body, the rabies virus targets nerve cells, leading to progressive and fatal encephalitis if left untreated. Despite notable progress in comprehending the illness

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and creating preventative methods, rabies continues to pose a significant public health issue, especially in areas with limited vaccination rates. Rabies virus infection causes severe brain inflammation in nearly all mammals, including humans, and is typically fatal once symptoms appear. The yearly worldwide mortality rate from rabies is roughly 59,000, with a disproportionate impact on neglected communities in Asia and Africa [1, 2].

The pathogenesis of rabies involves a complex interplay between the virus and the host's central nervous system (CNS) and plays a crucial role in determining the outcome of the infection. Following peripheral inoculation, typically via a bite from an infected animal, the virus travels along peripheral nerves to the CNS, where it exerts its pathogenic effects. This neurotropism is facilitated by the virus's ability to hijack the host's neuronal transport machinery, evading the immune system during the early stages of infection [3]. The initial immune response involves activating innate immune cells, such as macrophages and dendritic cells, which recognize the viral antigens and produce pro-inflammatory cytokines. Subsequently, adaptive immune responses, including the activation of T and B lymphocytes, are crucial for controlling viral spread and clearance. However, the rabies virus has evolved mechanisms to evade the host immune response, leading to a limited and delayed immune reaction, contributing to the disease's severity [2, 3].

Apoptosis, or programmed cell death, is a fundamental biological process critical in maintaining tissue homeostasis and eliminating damaged or infected cells [4]. In viral infections, apoptosis is a defense mechanism by eliminating virus-infected cells and limiting viral replication [5]. However, some viruses have developed strategies to manipulate the apoptotic pathway to their advantage by inhibiting apoptosis to prolong their survival within the host cell or inducing apoptosis to help spread and release viral [6]. The interplay between apoptosis and viral replication is particularly relevant in the case of rabies virus infection. The wild-type rabies virus has evolved sophisticated strategies to inhibit apoptosis in infected neurons, allowing it to evade immune responses and establish persistent infection within the CNS [7, 8]. This antiapoptotic property of the rabies virus is a key factor in its pathogenesis, contributing to the extensive neuronal damage observed in infected hosts.

Dexamethasone is a synthetic glucocorticoid effective in clinics due to its potent anti-inflammatory and immunosuppressive activities. It is used to treat autoimmune diseases, allergies, and some cancers. The drug regulates genes' transcription in immune responses, inflammation, and cell survival [9]. Although the therapeutic benefits of dexamethasone in reducing inflammation and immunomodulation have been well documented, its effects on viral infections, with specific reference to CNS infections, are complex and unclear [10, 11]. Its impact on viral infections remains poorly understood, particularly in the central nervous system (CNS). In rabies, a disease characterized by severe inflammation and neuronal death, dexamethasone's immunomodulatory effects could alter disease progression by potentially enhancing or inhibiting apoptosis, the programmed cell death mechanism. This is significant because the rabies virus evades the immune response, promoting viral persistence and reducing apoptosis in infected neurons [3].

Earlier studies have shown that glucocorticoids, such as dexamethasone, could impact the apoptosis pathways of host cells, which has likely implications for viral infections. Dexamethasone treatment may interfere with the viral strategy, whereby the rabies virus actively interferes with apoptosis to promote its survival, causing already infected neurons to suffer more apoptosis [12, 13]. This hypothesis raises essential questions about glucocorticoids' therapeutic and pathological relevance in treating viral encephalitis.

This research targets dexamethasone's potential for the apoptosis of brain cells in NMRI (Naval Medical Research Institute) mice infected with rabies virus. NMRI mice are an established model for studying rabies due to their susceptibility to the virus and the reproducibility of the infection's neurological effects. Here, we focus on the levels of apoptosis in these mice to find out how dexamethasone treatment would interplay with rabies virus-induced neuronal cell death. Thus, research into the role of dexamethasone in apoptosis following rabies virus infection would further serve to contribute views important for viral encephalitis management, including clinical decision-making under glucocorticoid therapy in such conditions. The findings of this study could have

significant implications for the risk-benefit ratio of glucocorticoid therapy in viral CNS infections and guide possibly more effective and safer treatment strategies.

2. Materials and Methods

2.1. Animal Model

2.1.1. NMRI mice

In this interventional research, after being approved by the ethics committee of the Pasteur Institute of Iran with code IR.PII.REC.1398.002, 72 female NMRI mice with an average weight of 17-20 grams (21 days old) were used and bought from the laboratory animal center of Pasteur Institute of Iran. NMRI mice are an outbred strain commonly used in research settings and are known for their genetic diversity. The mice were housed in standard conditions with free access to food and water. The room temperature was maintained between 20-25 degrees Celsius.

2.1.2. Experimental Design

Mice were randomly assigned to four groups (n=10 per group): a control group, a negative control group treated with dexamethasone, a positive control group infected with rabies virus without dexamethasone, and a test group infected with rabies virus and treated with dexamethasone.

2.2. Infection and Treatment

2.2.1. Rabies Virus Infection

Groups (3) and (4) were injected with the virus. According to the rabies laboratory techniques book, the mice were injected in the intracerebral (IC) route with 0.03 ml of wild rabies virus with 50 LD50 (lethal dose 50%). The virus was propagated in baby hamster kidney (BHK-21) cells and titrated to ensure consistent infection across all experimental animals.

2.2.2. Dexamethasone Treatment

Dexamethasone (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in sterile phosphate-buffered saline (PBS) and administered intraperitoneally at a dose of 1 mg/kg body weight daily for five consecutive days starting one-day post-infection. Control groups received an equivalent volume of PBS.

2.3. Tissue Collection and Processing

Five days after injection of the virus, a time point chosen based on preliminary studies that mice show triple rabies symptoms (paralysis, seizures, and irritability) were euthanized, and their brains were removed immediately and stored for subsequent studies in the -80ºC.

2.4. Fluorescent Antibody Test (FAT)

The presence of rabies virus in brain tissues was confirmed using the Fluorescent Antibody Test (FAT). Brain smears were made of the fixed tissue, air-dried, and acetone-fixed. The smears were incubated at 37°C for 30 min with a FITC-conjugated anti-rabies monoclonal antibody (Millipore, Billerica, MA, USA). Subsequent slides were washed with PBS for observation under a fluorescence microscope (Olympus, Tokyo, Japan). The FAT method utilizes fluorescently labeled antibodies that bind to the rabies virus antigens in brain tissue samples, enabling their visualization under a fluorescent microscope. This sensitive and specific method makes it a valuable tool for diagnosing animal rabies.

2.5. Molecular Analysis

2.5.1. RNA Extraction

Total RNA was extracted using the TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. The RNA concentration and purity were determined using a NanoDrop spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA).

2.5.2. cDNA Synthesis

Complementary DNA (cDNA) was synthesized from 5 µg of total RNA using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA) following the manufacturer's protocol.

2.5.3. Quantitative Real-Time PCR

Real-Time PCR was performed to quantify AKT, BAX, and BCL2 mRNA expression levels. The reactions were carried out in a 20 µL volume containing 10 µL of Power SYBR Green PCR Master Mix (Applied Biosystems), 5 µL of cDNA, and 0.5 µL each of forward and reverse primers (10 µM). The primer sequences used are shown in **Table 1**.

Table 1. Designed Primer sequences to investigate gene expression AKT, BAX, and BCL2 and house gene Sdha.

Genes	Forward Primer	Reverse Primer	Product length (nt.)
Sdha	5'-GGA GGT ATC AAT GCT GCT CTG-3'	5'-CTG TCA TGT AAT GGA TGG CGT-3'	118
BAX	5'-AGG ATG CGT CCA CCA AGA AG-3'	5'-GGA AGA AGA CCT CTC GGG G-3'	126
AKT	5'-AAC ACC TTT ATC ATC CGC TGC-3'	5'-TCT TGA GTC CAT CTG CCA CAG-3'	124
BCL2	5'-GAC TTC GCA GAG ATG TCC AGT-3'	5'-CAT CCC TGA AGA GTT CCT CCA-3'	91

The reactions were run on a QuantStudio 3 Real-Time PCR System (Applied Biosystems) under the conditions shown in **Table 2**.

Relative gene expression was calculated using the Δ Δ Ct method, normalizing to the housekeeping gene Sdha.

Table 2. Temperature program used in Real-Time PCR reaction.

Cycle/s	Time	Temperature (Degrees Celsius)	Cycle Step
One	15 min.	95	Initial denaturation
40	30 S.	94	Denaturation
	30 S.	60	Annealing
	20 S.	72	Elongation

2.6. Statistical analysis

Data were expressed as mean ± standard error of the mean (SEM). Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software. Differences between groups were assessed using one-way ANOVA followed by Tukey's post hoc test for multiple comparisons. A p-value of <0.05 was considered statistically significant. The LD50 (lethal dose 50%) was calculated using the Spearman-Karber method and appropriate statistical software. This method involves determining the dose of a substance that is lethal to 50% of the test subjects.

2.7. Ethical Considerations

All animal experiments were conducted strictly following the ethical guidelines set by the Pasteur Institute of Iran and were approved by the Institute's Animal Ethics Committee (Approval Code: IR.PII.REC.1398.002). The study adhered to the 'Guide for the Care and Use of Laboratory Animals' and made every effort to minimize animal suffering. Specific measures included using anesthesia where applicable, housing the animals in controlled environmental conditions, and ensuring that only the minimum number of animals required to achieve statistically significant results was used. Additionally, animals were monitored daily for signs of distress or illness, and humane endpoints were applied when necessary to prevent undue suffering.

3. Results and Discussion

3.1. Confirmation of Rabies Virus Infection by FAT

The presence of rabies virus antigens in the brain tissues of NMRI mice was confirmed using the Fluorescent Antibody Test (FAT). There were intense positive reactions to the staining against rabies virus antigens in the brain smears of infected mice, which indicated a successful infection. No viral antigens were detected in the brain tissues of uninfected control mice, further confirming the specificity of this infection. Such staining patterns are also observed in the case of both infected and uninfected dexamethasone-treated mice.

This indicates that dexamethasone administration does not interfere with viral antigen detection (**Figure 1**).

3.2. Effect of Rabies Virus Infection and Dexamethasone Treatment on Apoptotic Markers

AKT Expression: AKT, a vital cell survival mediator, was significantly increased in the infected versus the uninfected control mice ($p<0.01$). The effect of dexamethasone treatment on the AKT expression in rabies-infected mice significantly lowered, compared to untreated infected mice ($p<0.05$), suggesting that dexamethasone disrupts the virus's antiapoptotic strategy. The expression levels did not markedly change for AKT expression in dexamethasone-treated and untreated uninfected control mice (**Figure 2**).

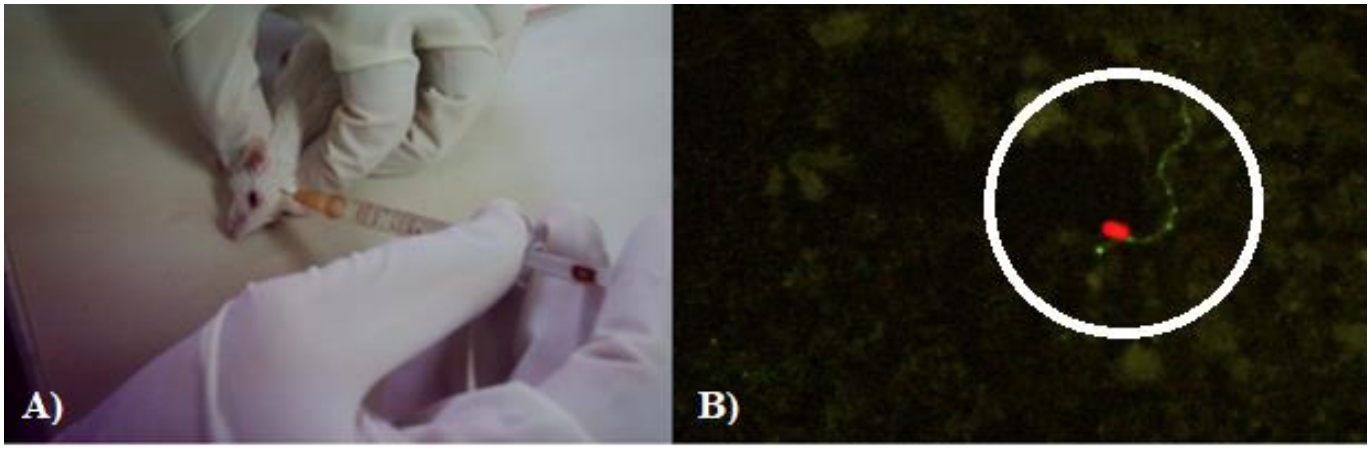

Figure 1. Polyclonal antibody reaction against the rabies virus nucleocapsid:

A) Each mouse in the test group was injected intracerebrally (IC) with 0.03 milliliters of wild rabies virus, titrated to 25 LD50. B) The FAT test yielded positive results, as indicated by the bright green spots observed around the face, which are due to the reaction of polyclonal antibodies conjugated with fluorescein binding to the rabies virus nucleocapsid.

BAX Expression: Pro-apoptotic protein BAX was reduced significantly ($p<0.01$) in the rabies-infected mice compared to uninfected controls. The BAX expression was increased in rabies-infected mice treated with dexamethasone compared to untreated infected mice ($p<0.01$), suggesting dexamethasone contributed to more intense pro-apoptotic signaling. Dexamethasone treatment alone did not significantly impact BAX expression in uninfected control mice (**Figure 2**).

BCL2 Expression: Rabies-infected mice showed considerably higher expression of BCL2, an antiapoptotic protein, than uninfected controls ($p < 0.01$). Dexamethasone therapy also significantly reduced the expression of BCL2 compared to infected mice without treatment ($p < 0.05$). There was no significant change in BCL2 expression between dexamethasone-treated and untreated uninfected control mice (**Figure 2**).

The BAX/BCL2 ratio was calculated to assess the apoptotic balance further. An increase in the BAX/BCL2 ratio signifies a shift toward pro-apoptotic signaling. The ratio in the infected mice was much lower than in controls ($p<0.01$), proposing consistency in the antiapoptotic strategies of the virus. However, infected mice treated with dexamethasone showed increased BAX/BCL2, which was significantly different from that of the untreated infected mice ($p<0.01$), which at least accounted for a movement of the balance towards the pro-apoptotic state due to dexamethasone. Results showed that the BAX/BCL2 ratio in dexamethasone-treated uninfected control mice and untreated ones was not statistically significantly different (**Figure 2**).

This current study was done to determine gene expression changes in dexamethasone treatment in the presence of rabies infection in mouse brain tissues. The data provide exciting insight into the complicated molecular interplay of dexamethasone treatment and rabies virus infection. Previous research demonstrated that the street rabies virus inhibits the process of cell death by regulating the expression of proteins involved in apoptosis.

More importantly, infection with RABV promotes the generation of anti-cell death proteins, including AKT and BCL2, that promote cell survival by lowering the effects of pro-cell death BAX proteins, thus enabling the persistence of RABV within the cell [8, 14]. However, this new study demonstrates that dexamethasone—another potent glucocorticoid—reverses the antiapoptotic effect described above by modulating the same markers associated with apoptosis.

Krakauer and Payne (1997) highlighted how viruses such as HIV use apoptosis to facilitate their spread and persistence within the host [5]. This finding parallels the strategy employed by the rabies virus, as discussed in our study, where it manipulates apoptotic pathways to promote its survival within the central nervous system.

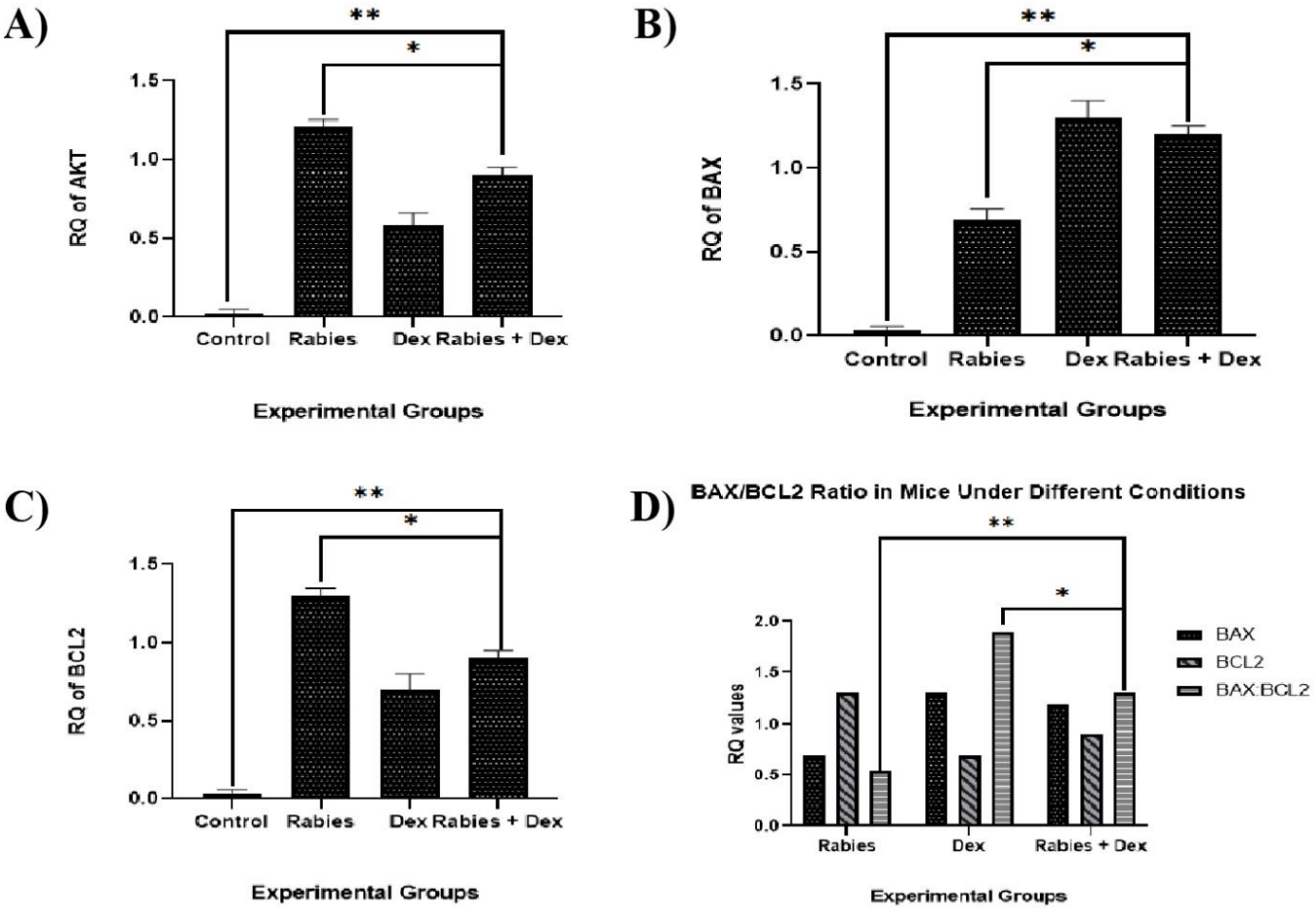

Figure 2. Changes in Gene Expression and BAX/BCL2 Ratio in Mice Under Different Conditions.
Groups: Control (uninfected), Rabies (infected), Dex (dexamethasone-treated uninfected control), and Rabies + Dex (infected and treated with dexamethasone).
(A) Relative Quantification (RQ) of AKT expression: The Rabies + Dex group showed a significant decrease in AKT expression compared to the Rabies group.
(B) RQ of BAX expression: The Rabies + Dex group exhibited a significant increase in BAX expression compared to the Rabies group.
(C) RQ of BCL2 expression: The Rabies + Dex group showed a significant decrease in BCL2 expression compared to the Rabies group.
(D) BAX/BCL2 ratio: The Rabies group had a lower BAX/BCL2 ratio compared to the control group ($p < 0.01$), indicating the virus's antiapoptotic strategy. However, the Rabies + Dex group had an increased BAX/BCL2 ratio compared to the untreated Rabies group ($p < 0.01$), suggesting a shift toward pro-apoptotic signaling due to dexamethasone treatment.
Note: Asterisks denote statistical significance (*$p < 0.05$, **$p < 0.01$).

FAT results proved that the rabies viral components were present in the brain tissue of infected NMRI mice; intense positive staining was observed. The result is consistent with and validates previous findings that the rabies virus established the infection. Somewhat surprising was that the viral component was not altered at all following the introduction of dexamethasone, indicating that dexamethasone does not interfere with the detection of the rabies viral component.

AKT is a critical player in promoting cell survival by inhibiting apoptosis. In the context of viral infections, including rabies, viruses often manipulate the AKT pathway to prevent host cell death, allowing the virus to persist and replicate within the host cells. The decrease in AKT expression observed in our study, particularly after dexamethasone treatment, indicates that dexamethasone may disrupt this viral strategy, promoting apoptosis and potentially aiding in the

clearance of infected cells. This shift in AKT expression is crucial because it marks a transition from a survival-promoting environment to one that favors cell death, which could limit viral replication [15].

BAX is a pro-apoptotic gene that promotes programmed cell death by increasing mitochondrial membrane permeability, releasing cytochrome c, and activating the caspase cascade. Viruses in viral infections like rabies tend to suppress BAX expression to evade apoptosis, allowing infected neurons to survive longer. In our study, dexamethasone treatment significantly increased BAX expression in rabies-infected mice, suggesting that the therapy promotes pro-apoptotic signaling, potentially reversing the virus's antiapoptotic effects [16].

BCL2, on the other hand, is an antiapoptotic gene that works to inhibit cell death by preventing the release of pro-apoptotic factors from the mitochondria. Viral infections often upregulate BCL2 to prolong host cell survival, creating a more favorable environment for viral replication. The reduction in BCL2 expression in our study following dexamethasone treatment further indicates a shift toward apoptosis. This suggests that dexamethasone counteracts the virus's attempt to suppress cell death, thus restoring the apoptotic balance [17].

AKT, BAX, and BCL2 expression are significant markers of cell apoptotic balance. Their regulation during viral infection can determine whether infected cells survive or undergo programmed cell death. The changes in these gene expressions in our study suggest that dexamethasone plays a critical role in shifting the balance toward apoptosis, which could be an essential mechanism in clearing rabies-infected neurons and mitigating the progression of the disease.

The study found that AKT expression significantly increased in rabies-infected mice compared to uninfected controls. This aligns with the virus's strategy to enhance cell survival and prevent apoptosis [18, 19]. However, dexamethasone treatment significantly lowered AKT expression in infected mice, suggesting that dexamethasone disrupts the virus-induced antiapoptotic mechanism. This finding indicates that dexamethasone may enhance apoptotic processes by downregulating AKT expression, essential for cell survival in rabies-infected cells. Noreen et al. (2021) discussed dexamethasone's broad therapeutic effects and limitations, particularly in the context of the COVID-19 pandemic. Their findings highlight how the immunosuppressive properties of dexamethasone can result in varying outcomes depending on the type of infection being treated [9]. This comparison is relevant to our study as it emphasizes the need to carefully evaluate dexamethasone's effects in viral infections like rabies, where its immunosuppressive action may influence disease progression differently.

BAX expression was significantly reduced in rabies-infected mice, reflecting the virus's ability to suppress pro-apoptotic signaling. Interestingly, dexamethasone treatment increased BAX expression in infected mice, suggesting that dexamethasone promotes pro-apoptotic signaling. This increase in BAX expression indicates that dexamethasone can counteract the virus's suppression of apoptosis, potentially leading to increased cell death in infected tissues.

Rabies-infected mice exhibited a substantial increase in BCL2 expression, consistent with the virus's strategy to inhibit apoptosis and promote cell survival. Dexamethasone treatment significantly reduced BCL2 expression in infected mice, further supporting the notion that dexamethasone shifts the balance towards apoptosis. The reduction in BCL2 expression underscores dexamethasone's role in diminishing the virus's antiapoptotic influence [20, 21].

The BAX/BCL2 ratio is a critical indicator of cell apoptotic balance. This ratio was markedly lower in infected mice than uninfected controls, confirming the virus's antiapoptotic strategy [19]. However, dexamethasone treatment increased the BAX/BCL2 ratio in infected mice, indicating a shift towards pro-apoptotic signaling. This significant change suggests that dexamethasone effectively counteracts the virus's suppression of apoptosis, potentially enhancing the clearance of infected cells.

Comparative analysis of the results with analogous research endeavors unveils a harmonious symphony in regulating apoptotic genes in response to viral incursions. These findings enrich our comprehension of the molecular intricacies underpinning viral pathogenesis and host immune responses. Moreover, they pave the way for alternative therapeutic avenues to recalibrate the host-pathogen interplay.

The stealthy maneuvers of the rabies virus to outmaneuver the host immune sentinels accentuate the exigency of tailored therapeutic interventions. Unveiling pharmaceutical agents capable of fine-tuning the expression of apoptotic genes, including AKT, BAX, and BCL2, holds promise in sculpting innovative strategies to combat viral onslaughts and fortify the host's defense arsenal against microbial adversaries [22, 23].

The findings of this study have significant implications for understanding the pathogenesis of rabies and the potential therapeutic use of glucocorticoids like dexamethasone. While the rabies virus employs strategies to prevent apoptosis and ensure its survival within the host, dexamethasone disrupts these mechanisms, leading to increased neuronal cell death.

Hyderabadi et al. (2020) explore the interplay between autophagy, apoptosis, and rabies virus infection, which supports the findings of our study on the role of apoptosis in rabies-infected neurons. Their research highlights similar cellular response mechanisms to rabies infection, providing a comparative perspective that aligns with the apoptotic changes observed in our study [18].

The increased apoptosis observed in dexamethasone-treated, rabies-infected mice could have pathological consequences. Excessive neuronal cell death can exacerbate CNS damage, contributing to the severe neurological symptoms and poor prognosis associated with rabies. These results underscore the need for caution when considering glucocorticoid therapy in viral encephalitis, as it may worsen disease outcomes by promoting apoptosis [20, 21].

The study highlights the complex interaction between glucocorticoid treatment and viral infections of the CNS. While dexamethasone is effective in managing inflammation, its use in the context of rabies and potentially other viral encephalitis must be carefully evaluated. The pro-apoptotic effects of dexamethasone could negate its anti-inflammatory benefits, leading to increased neuronal damage.

Future research should focus on elucidating the precise mechanisms by which dexamethasone influences apoptotic pathways in viral infections. Understanding these mechanisms could lead to targeted therapies that mitigate the pro-apoptotic effects of glucocorticoids while preserving their anti-inflammatory benefits. Additionally, exploring alternative immunomodulatory agents that do not enhance apoptosis could provide valuable insights into safer treatment options for viral encephalitis.

4. Conclusion

Overall, this study reveals the significant change effected by dexamethasone in the apoptotic pathway of brain tissue in infected mice. Dexamethasone weakens the ability of the virus to elude cell death through a decrease in AKT and BCL2 levels while increasing the expression of BAX, leading to apoptosis. These results thus lay a solid ground or basis regarding how dexamethasone might somehow be used to treat rabies virus infections through cell death stimulation in infected cells. Further studies are necessary to unveil the precise molecular mechanisms that mediate the effects of dexamethasone and to examine its clinical significance in treating rabies.

Conflict of interest

The authors declare to have no conflict of interest.

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There was no use of artificial intelligence in the making of this article.

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