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Rabies Virus Induced Blood Brain Barrier Disruption Mechanisms and Therapeutic Insights

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ABSTRACT

Rabies Virus (RABV) is a highly neurotropic pathogen whose near-uniform lethality reflects its capacity to invade the central nervous system by compromising the Blood Brain Barrier (BBB). This review synthesizes recent insights into the molecular and cellular mechanisms of RABV-induced BBB disruption organized around three themes: (1) viral trafficking and endothelial targeting; (2) host immune–barrier interactions, including pro-inflammatory cytokines and chemokines; and (3) extracellular-matrix remodeling, principally via Matrix Metalloproteinases (MMPs). We further discuss how specific mutations in the viral glycoprotein modulate MMP induction and barrier integrity and we propose translational strategies - MMP inhibitors, type III Interferon (IFN-λ) augmentation and targeted nanoparticle delivery - aimed at restoring BBB integrity without compromising antiviral immunity.

Keywords: Neuroinflammation, Therapeutic strategies, Neurotropic pathogen

Abbreviations: RABV: Rabies Virus; BBB: Blood Brain Barrier; CNS: Central Nervous System; MMPs: Matrix Metalloproteinases; ECM: Extracellular Matrix; IFN: Lambda Interferon Lambda; PEP: Post Exposure Prophylaxis; VNA: Virus Neutralizing Antibody; RIG: Rabies Immunoglobulin

1. Introduction

Rabies is a zoonotic viral disease that remains a major global health threat, causing an estimated 59,000 deaths annually, predominantly in low-resource regions. Most fatalities occur where access to timely medical care is limited. Once clinical signs appear, case fatality approaches 100%, with death typically occurring within days to weeks[1-5], underscoring the urgent medical need for improved prevention and control. Rabies Virus (RABV) is transmitted primarily via saliva-most commonly by animal bites or scratches-and the incubation period usually spans one to three months, although onset can range from a few days to several years after exposure[4-8]. Early symptoms are nonspecific

(fever, fatigue, headache), often followed by local paresthesia at the inoculation site[9,10]. Progressive neurologic manifestations include anxiety, agitation, insomnia and confusion, later advancing to dysphagia, laryngeal spasms, hydrophobia, muscle spasms, altered mental status and aberrant behavior[4,10,11]. The pathogenic mechanisms of rabies are complex and multifactorial; detailed mechanistic study is essential for the rational design of improved vaccines and therapeutics. Given the high mortality and continued burden of RABV infection, intensified research into pathogenesis, prophylaxis and treatment strategies remains a public-health imperative. In this review we adopt the abbreviations RABV and Blood Brain Barrier (BBB) after their first full appearance.

Rabies remains a preventable but lethal zoonosis, causing an estimated 59,000 human deaths annually worldwide, concentrated in Asia and Africa where timely access to Post-Exposure Prophylaxis (PEP) and dog vaccination is limited. Current PEP regimens combine active vaccination to elicit virus-neutralizing antibodies with passive immunization (rabies immunoglobulin) for high-risk exposures; when given promptly and correctly, PEP is highly effective at preventing clinical disease. Nevertheless, gaps in vaccine availability, cost and delivery infrastructure sustain the global burden. Integrating mechanistic insights into BBB disruption with approaches to enhance PEP efficacy and deliver targeted therapeutics may yield synergistic benefits for individual patient outcomes and public-health control.

Current rabies vaccines elicit Virus-Neutralizing Antibodies (VNAs) that principally target the viral Glycoprotein (G), blocking receptor binding and preventing neuronal entry. Post-Exposure Prophylaxis (PEP) combines active vaccination to induce VNAs with passive administration of Rabies Immunoglobulin (RIG) for severe exposures to provide immediate neutralization. Because BBB integrity limits antibody access once Central Nervous System (CNS) infection is established, there is a rationale for adjunctive approaches that enhance CNS delivery for example, transient, localized BBB modulation or targeted nanoparticle delivery paired with vaccination or therapeutic antibodies - to increase antiviral efficacy in the brain. Nevertheless, primary prevention remains paramount: mass dog vaccination, humane control of stray dog populations, public education and timely access to high-quality PEP are the most effective measures to reduce human rabies. Mechanistic insights into BBB disruption therefore open avenues for combination therapies in established CNS disease but should be pursued as complements to - not substitutes for - robust prevention and control programs.

2. Rabies Virus (RABV)

The RABV, a member of the family *Rhabdoviridae*, is a single-stranded, negative-sense RNA virus with a genome of ≈11,932 nucleotides. The genome encodes five structural Proteins-Nucleoprotein (N), Phosphoprotein (P), Matrix Protein (M), G and the RNA-dependent RNA polymerase (L)[12,13] each of which contributes interdependently to the viral life cycle, including replication, host-cell entry and immune evasion (Table 1).

Table 1: Key RABV structural proteins - functions, evidence linking to BBB disruption and therapeutic implications.

Protein	Main function	BBB-related mechanism	Key evidence (example refs)	Therapeutic implications
N (Nucleoprotein)	Genomic encapsidation; transcription template	Indirectly promotes neuroinflammation and cytokine release by increasing viral replicative burden	14-16	Target antivirals limiting replication; reduce downstream cytokine-driven BBB effects
P (Phosphoprotein)	Polymerase cofactor; IFN signaling antagonist	Inhibits type I IFN signaling (blocks STAT1 nuclear accumulation), compromising barrier integrity	22,23	Small molecules/vaccines/ nucleic-acid approaches to neutralize P and restore IFN responses
M (Matrix protein)	Virion assembly and budding; host signaling	Induces endothelial apoptosis and activates signaling pathways that disrupt tight junctions	24,25	Inhibitors preventing M-mediated dysregulation; limit virion egress
G (Glycoprotein)	Host cell entry; neurotropism; primary neutralizing antigen	Binds to BBB receptors and activates MMP2/9; specific amino acid changes alter BBB permeability	34,71-73	Vaccines/neutralizing antibodies targeting G; design attenuated G variants; inform antigen design
L (Large polymerase)	RNA transcription and replication; mRNA capping	Drives viral mRNA synthesis, indirectly exacerbating neuroinflammation	19,31,32	Polymerase inhibitors to reduce viral load and downstream inflammation

2.1. N: Genomic encapsulation and transcriptional regulation

The N nucleoprotein(N) encapsidates and stabilizes the viral RNA, forming a Ribonucleoprotein (RNP) complex that protects the genome from host nucleases and serves as the template for transcription and replication[14-16]. N interacts with the viral L to enhance enzymatic activity, thereby promoting efficient synthesis of viral mRNAs and progeny genomes[17,18].

2.2. P: Viral replication and immune evasion

The P Phosphoprotein (P) is an essential cofactor for L: it recruits L to the RNP complex and promotes viral transcription and replication[18-20]. In addition, P antagonizes host interferon signaling, impairing innate antiviral responses and facilitating viral persistence[21-23].

2.3. M: Virion assembly and host immune modulation

The M Matrix Protein (M) orchestrates virion assembly and budding by bridging interactions between N and G and by associating with the host plasma membrane during egress[24]. M additionally modulates host signaling pathways to blunt antiviral defenses and contribute to pathogenicity[3,25,26].

2.4. G: Host cell entry and neurotropism

The G glycoprotein (G) is the principal surface protein responsible for receptor engagement and membrane fusion[24,27]. G binds neuronal receptors (e.g., nicotinic acetylcholine receptor, neurofascin-1), mediating adsorption and endocytosis into target cells; in the acidic endosome G undergoes conformational change to drive membrane fusion and genome release. Because

G is the principal target of virus-neutralizing antibodies, it is central to vaccine design and serological protection[28,29].

2.5. L: Viral genome transcription and replication

The L protein executes viral RNA synthesis in complex with P and the RNP, catalyzing both transcription and replication[22,23,30,31]. L also carries enzymatic activities required for mRNA capping and methylation, processes that stabilize viral transcripts and enable efficient translation of viral proteins[17,32]. L expression and activity are temporally coordinated with late-stage viral assembly and release[31].

2.6. RABV infection in neurons

RABV pathogenesis reflects a neuron-tropic replication strategy that exploits peripheral entry sites and axonal transport to evade immune surveillance and disseminate within the CNS[33,34]. Following peripheral exposure, viral particles first infect muscle and local cells at the wound site. The viral G mediates attachment to host receptors (for example, nicotinic acetylcholine receptors) and promotes receptor-mediated endocytosis; acidic endosomal conditions then trigger G-mediated membrane fusion and release of the RNP into the cytoplasm, where it serves as the template for transcription and genome replication[33,35-37]. Viral mRNAs are translated and structural proteins are produced, after which progeny RNPs assemble and budding occurs at cellular membranes.

Newly formed virions or nucleocapsids access peripheral nerve terminals and undergo retrograde axonal transport to the spinal cord and brain. Within the CNS, RABV spreads trans-synaptically to infect neuronal circuits, producing progressively higher viral loads and ultimately causing neuronal dysfunction and encephalitis[33,34]. During this process the virus minimizes cytolytic cell death and delays robust adaptive immune detection, facilitating widespread intraneuronal replication.

Neuronal infection elicits innate immune activation: infected neurons and glia produce cytokines and chemokines that recruit and activate microglia and astrocytes, amplifying neuroinflammatory responses that interact with BBB function[33]. The balance between viral propagation along neural pathways and host innate and barrier responses critically determines disease trajectory and clinical outcome.

3. Blood Brain Barrier (BBB)

The BBB is a highly selective interface that separates the CNS from the systemic circulation and maintains the brain's microenvironment[38-40]. Its principal functions are to restrict the entry of toxins and pathogens, regulate transcellular and paracellular transport and ensure delivery of essential nutrients and signaling molecules. Structurally, the BBB is defined by tightly interconnected endothelial cells that impede the passage of large and polar solutes while permitting passive diffusion of small lipophilic compounds and supporting carrier-mediated uptake of glucose, amino acids and other vital substrates[38,41-44].

The BBB is a multicellular unit comprising brain endothelial cells, pericytes, astrocytes and other glial elements[39,45-55]. Brain endothelial cells display high polarity and a specialized repertoire of transporters and receptors on their luminal and abluminal membranes and they form continuous tight junctions that limit paracellular flux[47-50]. Pericytes closely oppose the endothelium and are critical for BBB development and structural stability, modulating endothelial permeability and vascular tone[51-53]. Astrocyte end-feet ensheathe the vasculature and secrete factors that promote barrier function; microglia and other glia contribute via cytokine and growth-factor signaling to maintain or remodel barrier properties[54,55].

BBB permeability is dynamic and context dependent. While increased permeability can improve delivery of immune effectors and therapeutics to the CNS, it also permits ingress of pathogens and circulating toxins, thereby increasing the risk of neural injury (Figure 1). Thus, BBB disruption represents a double-edged sword: it may aid pathogen clearance by allowing immune access, yet simultaneously exacerbate neuroinflammation and neuronal damage if barrier integrity is not restored[55-59].

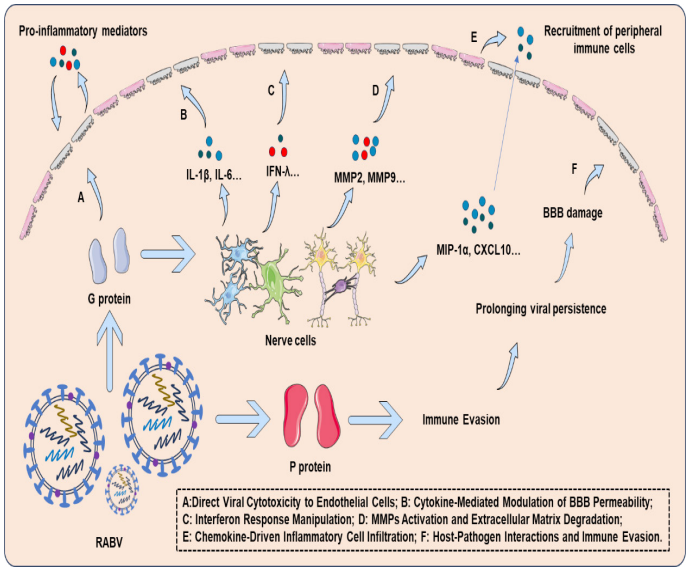

Figure 1: Graphical summary of the molecular mechanism of RABV breaking the BBB.

4. Mechanisms Underlying BBB Disruption by RABV

RABV compromises BBB integrity through a combination of direct viral actions on barrier cells, secondary host immune responses and altered intercellular regulatory signaling. Loss of barrier function increases paracellular and transcellular permeability, permits leukocyte and protein influx and thereby amplifies neuroinflammation and neuronal injury. The subsections below summarize the principal mechanisms implicated in RABV-mediated BBB disruption.

4.1. Direct viral cytotoxicity to endothelial cells

RABV directly affects brain microvascular endothelial cells and thereby undermines BBB structural integrity. The viral G, which mediates receptor binding and entry, also stimulates endothelial pro-inflammatory signaling and can promote endothelial dysfunction. G-dependent activation of endothelial cells induces the release of cytokines and other mediators that compromise tight-junction complexes, increase endothelial apoptosis or dysfunction and elevate paracellular permeability-permitting influx of circulating immune cells and plasma proteins into the CNS and exacerbating neuroinflammation and neuronal injury[60-62]. In addition, infected neurons secrete soluble factors that further perturb endothelial function and enhance barrier leakage, facilitating local viral spread into adjacent brain tissue[63,64]. Collectively, these direct viral effects create a permissive environment for intraparenchymal replication while amplifying the inflammatory milieu.

4.2. Cytokine-Mediated modulation of BBB permeability

RABV infection provokes release of proinflammatory cytokines-notably interleukin-1β (IL-1β) and interleukin-6 (IL-6)-from infected neurons and activated glia (microglia, astrocytes) and these mediators are central drivers of BBB dysfunction. IL-1β is produced as a 31-kDa precursor (pro-IL-1β) that is cleaved by caspase-1 to yield the bioactive cytokine, which promotes barrier disruption in part by degrading tight-junction proteins and increasing paracellular permeability[65,66]. In murine models, recombinant RABV engineered to express IL-1β increases animal survival relative to wild-type virus, an effect ascribed to enhanced recruitment of peripheral immune effectors (including CD4+ T cells) and reduced CNS viral load secondary to transient BBB opening[67]. Similarly, IL-6 is strongly associated with increased BBB permeability: recombinant RABV expressing IL-6 produces an early, pronounced elevation in barrier leakiness compared with parental strains, thereby facilitating immune cell entry and viral clearance but also amplifying neuroinflammation[59,68-70]. Together, IL-1β and IL-6 illustrate a double-edged role for cytokine-driven BBB modulation-promoting antiviral immunity via increased immune access while risking collateral inflammatory injury to neural tissue.

4.3. Interferon response manipulation and immune modulation

Interferons (IFNs) are central to antiviral defense, yet RABV subverts IFN signaling to facilitate CNS persistence. In particular, type III interferons (IFN-λ) have been implicated in limiting RABV pathogenicity by dampening excessive inflammation and preserving barrier integrity. Recombinant RABV engineered to express IFN-λ shows reduced induction of proinflammatory cytokines and chemokines, reduced BBB permeability and decreased leukocyte infiltration into the CNS, consistent with a protective, barrier-stabilizing role for IFN-λ in rabies models[71]. These data position IFN-λ-based modulation as a potential therapeutic strategy to limit neuroinflammation while preserving antiviral immunity.

4.4. Matrix Metalloproteinase Activation and Extracellular Matrix Degradation

Matrix Metalloproteinases (MMPs), especially MMP-2 and MMP-9, degrade extracellular matrix components and disrupt endothelial tight junctions, thereby increasing BBB permeability. RABV infection upregulates MMP expression in endothelial and immune cells and the viral G has been implicated as an upstream activator of signaling pathways that drive MMP induction[34]. Viral genetic variation can modulate this effect: specific residues in G influence its activity and downstream MMP responses. For example, substitutions at position 38 alter G expression and thereby affect MMP induction, while a glycine-alanine substitution at residue 349 (G349A) has been reported to further increase BBB permeability; intriguingly, this mutation increases immune activation yet attenuates viral pathogenicity in murine models[72,73]. Together, these findings underscore how viral sequence variation in G shapes host protease responses and the consequent integrity of the neurovascular barrier.

4.5. Chemokine-Driven inflammatory cell infiltration

Chemokines both recruit immune cells to the CNS and contribute to BBB disruption during RABV infection. Upregulation of chemokines such as macrophage inflammatory protein-1α (MIP-1α), regulated on activation normal T cell expressed and secreted (RANTES) and C-X-C motif chemokine ligand 10 (CXCL10) promotes influx of T cells, macrophages and dendritic cells into infected brain regions, which can amplify barrier breakdown, neuroinflammation and neuronal injury. RABV strains differ in their chemokine-inducing capacity: many laboratory-adapted strains evoke strong chemokine responses that increase immune cell entry and BBB permeability. While this response can accelerate viral clearance, excessive or dysregulated chemokine signaling causes immunopathology in a context- and strain-dependent manner. For example, MIP-1α expression is associated with reduced viral burden and enhanced dendritic-cell recruitment and activation, thereby boosting adaptive immunity[74,75]. By contrast, RANTES and CXCL10 have been linked to worsened disease in some settings[75-78]; however, recombinant RABV engineered to express CXCL10 can increase early BBB permeability and thereby facilitate immune-mediated viral clearance, paradoxically reducing pathogenicity in certain models[64]. Together, these data underscore a nuanced role for chemokines in rabies: they are essential for antiviral defense but can also drive harmful neuroinflammation when excessively induced.

4.6. Host-Pathogen interactions and immune evasion

RABV sustains central nervous system infection by deploying immune-evasion strategies that permit prolonged viral replication and persistent compromise of the BBB. The P is a principal immunomodulator: by antagonizing type I interferon signaling it blunts early antiviral responses, delays immune recognition and thereby extends intraneuronal viral survival. This immune subversion not only facilitates viral spread within the CNS but also promotes dysregulated inflammation and increased BBB permeability. The interplay between viral immune modulation and host inflammatory responses therefore complicates therapeutic design, since interventions must enhance antiviral clearance without exacerbating collateral neuroinflammation or barrier injury.

5. Intervention Strategies and Translational Opportunities

The multifactorial mechanisms driving RABV-induced Blood Brain Barrier (BBB) disruption suggest several complementary intervention avenues:

(a) MMP inhibition: Selective blockade of MMP-2 and MMP-9 may preserve extracellular matrix and tight-junction integrity, limiting pathological leukocyte entry. Preclinical viral-encephalitis models indicate that MMP modulation can reduce barrier breakdown and neuroinflammation; however, careful dosing and timing are required to avoid impairing beneficial immune cell trafficking.

(b) IFN-λ augmentation: Exogenous IFN-λ upregulates interferon-stimulated genes at the neurovascular interface, sustains tight-junction protein expression and can attenuate RABV replication and neuroinflammation in experimental systems. Localized or systemic IFN-λ-potentially combined with standard immunotherapies-warrants evaluation in rigorous preclinical challenge models.

(c) Chemokine modulation and immune-restoration: Precision modulation of chemokine networks (for example,

restraining excessive CXCL10 or RANTES signaling while preserving dendritic-cell–recruiting CCL3/MIP-1α activity) could limit pathological infiltration without compromising antiviral immunity. Parallel strategies to neutralize viral immune-evasion factors (e.g., inhibitors or immunogens targeting the P protein to restore type I IFN signaling) may further enhance host control.

(d) Nanoparticle-facilitated, BBB-targeted delivery: Ligand-directed nanoparticles offer a route to concentrate MMP inhibitors, interferons or antiviral agents at the neurovascular unit, increasing local efficacy and reducing systemic exposure.

In sum, a translational framework that combines pathogen-directed antivirals/immunogens with host-directed therapies (MMP modulation, IFN-λ augmentation, chemokine balancing), delivered where feasible via targeted nanocarriers, should be tested in staged preclinical models that measure both viral clearance and preservation of neural tissue.

6. Conclusion

RABV compromises BBB integrity through multiple, converging mechanisms - direct endothelial injury, cytokine-driven increases in paracellular permeability, MMP-mediated extracellular-matrix degradation and chemokine-directed leukocyte recruitment - which together amplify neuroinflammation and neuronal damage. These mechanistic insights highlight several host-directed intervention opportunities (for example, selective MMP modulation, IFN-λ augmentation and precision chemokine targeting) that could be deployed alongside antiviral or immunotherapeutic strategies to limit CNS invasion while preserving protective immunity. Critically, translational evaluation must assess both viral clearance and neural preservation in rigorously characterized preclinical models and quantify trade-offs between improved barrier integrity and necessary immune trafficking. Prioritizing interventions that restore BBB homeostasis without compromising antiviral defenses should be a central aim of future work. Elucidating the molecular determinants by which viral genes (notably glycoprotein and phosphoprotein) and host pathways (cytokines, MMPs, chemokines, interferons) interact to shape barrier function will accelerate rational design of adjunctive therapeutics for rabies and other neuroinvasive viral infections.

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