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The biology of virally initiated pain states

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Virally initiated pain states occur across a wide range of species and viral families, but the mechanisms by which viral infection produces acute or chronic pain remain incompletely understood. This perspective is based on the presentation, "The Puzzle of Virally Induced and Sustained Pain States", delivered at the 2025 International Veterinary Emergency and Critical Care Symposium (IVECCS) held in San Diego, California, September 4–8, 2025. Drawing on representative viral models, this perspective organizes mechanisms of virally initiated pain into three overlapping routes: direct neuronal infection or receptor activation, indirect modulation through non-neuronal and immune cells within infected tissue, and systemic immune signaling originating outside of the nervous system. By highlighting shared and distinct mechanisms across viral models, this comparative framework aims to guide mechanistic investigation and identify potential therapeutic targets for virally initiated pain across human and veterinary medicine.

KEYWORDS
FIV, influenza a virus, neuroimmune activation, nociceptor, pain, SARS- CoV- 2, SIV, viral infection

Introduction

Viral infection is a potent and prevalent initiator of pain states (1, 2). In humans, human immunodeficiency virus (HIV) (3) can drive neuropathies, and varicella-zoster virus (VZV) (4) causes shingles and post-herpetic neuralgia. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can drive persistent pain states and other neurological sequelae, serves as another timely example (5). Virally initiated pain also affects companion animals, laboratory animals, exotics, and livestock. Studying these conditions across species can inform human medicine, improve animal welfare, and address production losses in livestock.

In dogs, canine parvovirus infection can be characterized by abdominal pain (6, 7). Canine distemper can lead to pneumonia-associated pain (8, 9) and chronic neurological damage (10). In cats, certain strains of feline calicivirus (FCV) are associated with chronic gingivostomatitis (11–14) or polyarthritis (15). Feline immunodeficiency virus (FIV) in cats leads to distal sensory polyneuropathies similar to those caused by HIV in humans (16, 17). FIV is also associated with intractable stomatitis and oral pain (18).

Laboratory models of virally initiated pain and sensory dysfunction include influenza A virus (IAV), VZV, and HIV models in mice and rats, and SARS-CoV-2 infection in hamsters (19–22). Among exotics, nonhuman primates, including macaques, have long served as models for chronic HIV-associated sensory neuropathy following simian immunodeficiency virus (SIV) infection (19). Further, "elephant pox", resulting from orthopoxvirus infection, causes ulcerative lesions on the skin and on mucosal membranes (23). Regarding livestock, reovirus induces viral arthritis in chickens and

represents a significant economic burden (24) to the poultry industry; this virally initiated pain state has been compared to human rheumatoid arthritis (25). Parapoxvirus infection can lead to contagious ecthyma in sheep and goats (26), characterized by painful pustular sores and oral lesions impairing eating and weight gain.

These conditions can present as acute or chronic, localized or diffuse pain during infection or after its resolution. Across this breadth of clinical manifestations, the underlying mechanisms remain poorly understood, and effective therapies are limited.

This perspective builds on the presentation, "The Puzzle of Virally Induced and Sustained Pain States", delivered at the 2025 International Veterinary Emergency and Critical Care Symposium (IVECCS) held in San Diego, California, September 4–8, 2025.

The presentation addressed the assessment, cellular mechanisms, and treatment implications of virally initiated pain. To examine how viruses cause pain, we focus on four models for which mechanistic data are comparatively rich: FIV and SIV, SARS-CoV-2, and IAV. Although central mechanisms also contribute to pain, this perspective focuses primarily on peripheral sensory neurons and local or systemic signals that alter their function. We organize these mechanisms into three overlapping routes: direct infection or activation of sensory neurons, indirect effects mediated by local non-neuronal and immune cells, and systemic immune signaling acting on the nervous system from a distance. This framework may generalize to virus-associated pain states that remain mechanistically undefined and help guide therapeutic development and treatment. Before examining these mechanisms, we first consider how pain is assessed in animals.

Evaluation of pain

Over the last two decades, methods for the evaluation of pain in animals have advanced considerably (27–29). In clinical settings, assessment relies on changes in demeanor, activity, and pain-associated behaviors like guarding, licking, biting, scratching, and vocalization. Standardized behavioral pain scoring systems help clinicians quantify these observations and monitor changes over time (8). In experimental settings, behavioral assays often measure responses to controlled stimuli. FIV-induced sensory neuropathy in cats, for example, has been characterized by delayed withdrawal responses to thermal and mechanical stimuli (17, 30, 31), whereas SARS-CoV-2 and IAV-associated sensory abnormalities in hamsters have been characterized through mechanical hypersensitivity (21). These examples illustrate that sensory dysfunction can manifest as either increased or decreased responsiveness, depending on the fibers affected, disease stage, and assay modality, but neither outcome independently establishes the presence of pain.

Interpretation of these measures is further complicated by several factors. Clinical observations can be subjective, while motor dysfunction can alter withdrawal responses and reduced activity may reflect depression. These limitations are particularly relevant when interpreting cross-species or cross-model comparisons, where differences in assay sensitivity rather than true mechanistic differences may account for discrepant findings. Complementary physiological and biochemical readouts include respiratory rate, heart rate, blood pressure, temperature, electromyography and plasma concentrations of substance *P* and cortisol (27), although these are also not specific to pain.

Behavioral and clinical assays also cannot identify the cellular mechanisms underlying these outcomes. Consequently, studies frequently combine behavioral phenotyping with histological, transcriptomic, electrophysiological, and molecular analyses to identify how specific viruses perturb nociceptor biology. These mechanistic studies form the focus of the following sections.

The physiology of pain and viral infections

The following paragraphs are simplifications of how nociception and viral infection may proceed. We then discuss how these processes can overlap to induce virally initiated and sustained pain states.

Nociception is the process of detecting and relaying stimuli that damage tissue or have the potential to damage tissue. Nociceptive signals are transmitted from the peripheral nervous system (PNS) to the central nervous system (CNS) for higher-order processing (32) (Figure 1). The cell bodies of spinal nociceptors reside within the dorsal root ganglion (DRG) and axons extend into the periphery (Figure 1A) and spinal cord (Figure 1B). Nociceptors convert noxious peripheral stimuli into electrical signals that propagate to the spinal cord (Figure 1B), where they synapse onto second-order neurons that relay the signal to the brain for higher-order processing (Figure 1C). The descending pathway initiating from the rostral ventromedial medulla can exert bidirectional modulation on this nociceptor-mediated ascending pathway (33). Overactivation or dysregulation of these processes can contribute to pathological or chronic pain states. DRG macrophages regulate nociceptor excitability and spinal microglia modulate dorsal horn transmission (34). Moreover, unlike the blood-brain barrier, that of the DRG is permeable to circulating factors like cytokines, chemokines and immunoglobulins (IgGs) (35). Local and systemic inflammatory factors can directly sensitize nociceptors (36), lowering activation thresholds, often through phosphorylation or altered trafficking of ion channels such as transient receptor potential channels (ex. TRPV1, TRPA1) and voltage-gated sodium channels (ex. NaV1.7, NaV1.8), thereby increasing neuronal excitability and spontaneous firing. Sustained peripheral input can also promote central sensitization, increasing responsiveness of central nociceptive circuits and amplifying nociceptive signaling.

Viral infection begins with the attachment of viral particles to permissive host cells. This tropism is largely determined by whether the host cell expresses attachment factors and entry receptors compatible with viral surface proteins (37). After attachment and entry, the virus co-opts host cellular machinery to replicate and produce new virus. This infection within a host cell may lead to host cell transcriptional/translational

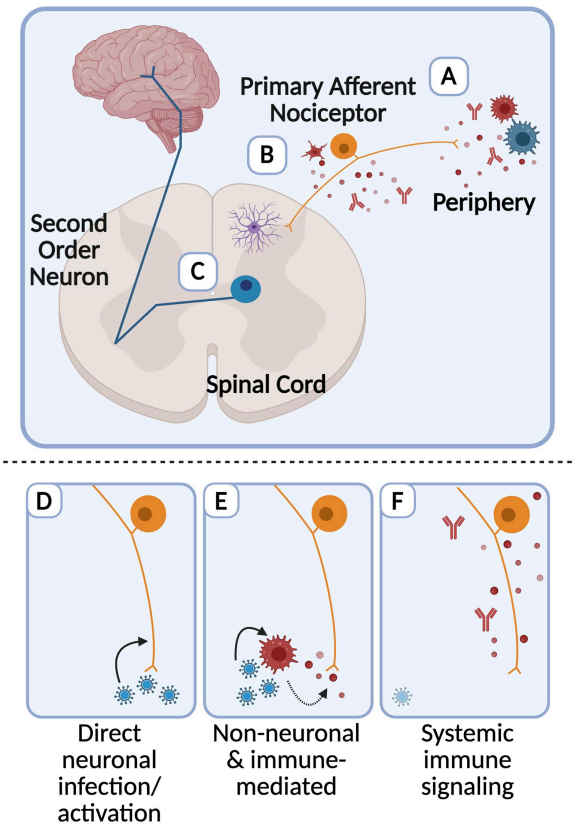


FIGURE 1
Nociceptive signaling and mechanisms of virally initiated pain. (Top) Overview of nociceptive signaling. (**A**) A spinal nociceptor detects noxious stimuli through its peripheral terminal. (**B**) Its cell body resides in the dorsal root ganglion (DRG), and its central axon relays signals into the spinal cord. (**C**) The nociceptor synapses onto a second-order neuron that relays the signal to the brain. DRG macrophages regulate nociceptor excitability, while spinal microglia modulate dorsal horn transmission. The DRG's vascular barrier permits circulating immune factors to act directly on the nociceptor. (Bottom) Three overlapping mechanistic categories of virally initiated pain. (**D**) Direct neuronal infection or activation alters neuronal excitability or viability (e.g., SARS-CoV-2). (**E**) Infection or activation of resident non-neuronal or immune cells, such as macrophages, leads to the release of inflammatory mediators that alter neighboring nociceptor function (e.g., FIV and SIV). (**F**) Systemic immune signaling involves circulating mediators originating at a distant site that act on the nociceptor without requiring local infection (e.g., influenza A). These categories are not mutually exclusive and illustrate mechanisms supported by the representative models summarized in Table 1. Created in BioRender. Dochnal, S. (2026) https://BioRender.com/0t3f0yj.

reprogramming, damage, or death (38–40). Viral infection is often accompanied by the activation of innate and adaptive host immunity involving populations of natural killer (NK) cells, macrophages, and T and B lymphocytes (41). Immune activation releases cytokines, chemokines, and antibodies, which can contribute to clearing the infection. However, not all infections are effectively cleared after primary infection and acute replication. Some viruses, like herpesviruses and retroviruses, can establish persistent infections with latent reservoirs within a specialized host cell type (42). Viral reactivation can subsequently cause disease, including pain (43).

How can a virus cause pain? Shared and divergent mechanisms across viral models

Viruses can alter nociceptive function through three overlapping cellular routes, consistent with a broader pathogen-nociceptor framework (44). First, direct neuronal infection or activation may alter nociceptive signaling through changes in excitability, injury, or death. Second, infection or activation of resident Schwann cells, macrophages, or other non-neuronal cells within infected tissue can alter the release of cytokines, chemokines, growth factors, and other mediators that modulate neuronal excitability. Third, viral infection may drive systemic immune activation, with circulating inflammatory mediators from a distant site acting on nociceptors without requiring local infection of neuronal or non-neuronal cells.

These mechanisms are illustrated as three categories in Figure 1 and summarized across four viral models in Table 1. Individual viruses map onto a small set of recurring mechanistic categories, a framework that may help generate hypotheses about the many pain-associated viruses for which mechanistic data remain limited.

FIV infection provides a well-characterized model of chronic sensory polyneuropathy in cats. The Power laboratory demonstrated sensory dysfunction persisting for up to 12 weeks post-infection, characterized by delayed withdrawal responses and mechanical hyposensitivity consistent with sensory loss (17, 30, 31). Although FIV is readily detected within peripheral nerves, the virus infects immune cells rather than sensory neurons. Infection is accompanied by macrophage accumulation within the sciatic nerve and DRG, together with progressive axonal atrophy and loss of sensory fibers (17).

Using an *ex vivo* co-culture of DRG neurons, Schwann cells, and macrophages (16), the Power laboratory further demonstrated that FIV infection of macrophages induces STAT1, iNOS, and TNF-alpha activation, while pharmacological inhibition of iNOS protects neighboring neurons from injury. Another macrophage-to-neuron injury pathway involves IL-1beta released by infected DRG macrophages, which increases protease-activated receptor-1 (PAR1) expression in sensory neurons, driving neurite retraction; blocking IL-1beta signaling prevents this *in vitro*. *In vivo*, FIV infection increased macrophage IL-1beta, neuronal PAR1 expression, and mechanical hyposensitivity (30). A distinct immune-cell population may also contribute to this injury: T lymphocytes infiltrate the DRG during FIV infection, and CD8+ T cells isolated from infected animals injure cocultured sensory neurons through contact/CD154-dependent toxicity, causing neurite shrinkage and soma atrophy (45). Together, these studies identify multiple immune-mediated pathways linking FIV infection to sensory-neuron injury and loss of sensory function.

Similar patterns of immune-associated sensory neuropathy have been observed in SIV-infected macaques. SIV-associated peripheral neuropathy has been characterized through structural, electrophysiological, and molecular endpoints: intraepidermal nerve fiber density, DRG histopathology, altered C-fiber nerve conduction velocity (46), and transcriptomic/immunohistochemical profiling (47).

Despite antiretroviral therapy (ART), SIV-infected macaques exhibit increased immune cell infiltration and inflammatory cytokine expression within the DRG, accompanied by increased neuronal expression of TRPV1 and TRPA1 and reduced innervation of non-peptidergic nociceptors (47, 48), a molecular profile consistent with nociceptor sensitization. This TRPV1 upregulation appears to be driven in part by IFN-gamma-inducible chemokines: DRG transcriptomic profiling identified persistent CXCL9/CXCL10 signaling despite ART, and CXCL10 alone and combined CXCL9/CXCL10 directly induced TRPV1 expression in sensory neurons *in vitro*, establishing a candidate macrophage-to-neuron signaling axis that may explain why nociceptor sensitization persists despite controlled viral replication (49). Together, FIV and SIV illustrate how infection and activation of immune cells can drive nociceptor dysfunction and neuropathy (50).

Respiratory SARS-CoV-2 infection of hamsters produces persistent mechanical hypersensitivity, providing an experimental model relevant to post-COVID sensory abnormalities (21, 51). In contrast to lentiviruses, SARS-CoV-2 may directly infect sensory neurons, where viral RNA and protein have been detected alongside transcriptional changes associated with axonal injury, altered excitability, and neuropathic pain (21, 52–54). Evidence further suggests that direct infection of TRPV1-expressing sensory neurons drives upregulation and redistribution of TRPV1 itself, contributing to axonal degeneration (55).

Viral proteins can also alter nociceptive signaling without productive neuronal infection. SARS-CoV-2 papain-like protease activates airway-innervating trigeminal and vagal nociceptors in mice and human iPSC-derived nociceptors, and induces TRPA1-dependent sneezing and nociceptive behaviors in mice (56). A viral envelope protein and spike receptor-binding domain can trigger nociceptive behavior via TLR2 or TLR4-MyD88 signaling in the DRG and dorsal horn (57). Because TLR2 and TLR4 can be expressed by both sensory neurons and immune cells, these effects may involve direct neuronal signaling as well as immune-mediated pathways (58, 59). Collectively, these findings support direct neuronal infection or activation as potential contributors to SARS-CoV-2-associated sensory dysfunction, alongside signaling involving non-neuronal and immune cells.

In contrast to the direct neuronal mechanisms implicated in SARS-CoV-2-associated sensory dysfunction, IAV-associated hypersensitivity can arise through systemic immune signaling without neuronal infection. Although certain IAV strains are neurotropic, neuronal infection is not required for mechanical hypersensitivity in rodents (60–62). Transcriptomic analysis of thoracic DRGs from infected hamsters reveals a predominantly pro-inflammatory signature, contrasting with the neuronal transcriptional changes observed following SARS-CoV-2 infection (21). Consistent with a systemic route of action, IAV infection in mice induces mechanical hypersensitivity through an indoleamine 2,3-dioxygenase (IDO1)-dependent pathway. Infection stimulates IDO1 expression in lung and lymphoid tissue, generating kynurenine, which is sufficient to induce pain hypersensitivity independent of infection (22). Type I interferons provide another potential link between antiviral immunity and nociceptor sensitization: experimental exposure to IFN-alpha or -beta produces neuronal hyperexcitability and mechanical hypersensitivity through MNK-eIF4E signaling (63). Together, these findings support immune signaling initiated outside the nervous system as a contributor to influenza-associated sensory dysfunction.

Together, these models illustrate how distinct viral and immune mechanisms can converge on altered sensory-neuron function, often through overlapping pathways.

Discussion: treatments and therapeutic considerations

As summarized in Table 1, diverse viral families engage overlapping cellular pathways that may provide targets for intervention, although most mechanism-targeted approaches remain investigational for virus-related pain.

Pain driven by direct neuronal infection may benefit from antiviral therapies capable of limiting viral replication or neuronal infection, such as nucleoside analogs. SARS-CoV-2 illustrates two targets for antiviral intervention: neuronal infection and activation of the nociceptor by viral protein components. Because these viral proteins are themselves products of active replication, antiviral therapy would be expected to reduce both modes by limiting the overall supply of virus and viral protein.

TABLE 1 Shared and divergent mechanisms of virally initiated pain across models.

Virus	Species	Direct neuronal infection?	Mechanism	Key mediators	Sensory/pain phenotype
FIV	Cat	No	Macrophage- and T cell-mediated inflammation	STAT1, iNOS, TNF-alpha, IL-1beta, PAR1, CD154	Chronic neuropathy (sensory loss)
SIV	Macaque	No	DRG immune activation	TRPV1, TRPA1, CXCL9, CXCL10	Chronic neuropathy (no behavioral data)
SARS-CoV-2	Hamster/ Mouse/Human	Potentially	Direct neuronal infection or activation; viral protein sensing through neuronal and immune pathways	TRPV1, TRPA1, TLR2, TLR4, MyD88	Persistent mechanical hypersensitivity
Influenza	Hamster/ Mouse	Not required for hypersensitivity	Systemic inflammatory signaling	IDO1, kynurenine	Acute hypersensitivity

Pain arising through infection or activation of non-neuronal regulatory cells may be more amenable to therapies targeting these locally acting mediators directly, such as iNOS inhibition or anti-TNF-alpha therapies. Likewise, pain initiated by systemic inflammatory responses may benefit from interventions that target these systemic drivers directly, such as IDO1 inhibition, or that dampen inflammatory signaling more broadly, such as corticosteroids.

However, antiretroviral therapy alone does not necessarily prevent or resolve viral pain. Longitudinal human studies demonstrate persistent and newly developing HIV-associated neuropathic pain despite high rates of viral suppression (64). Consistent with these clinical observations, SIV + macaques maintained on ART continue to exhibit DRG immune infiltration and altered nociceptor gene expression (47). In some cases, antivirals may exacerbate the condition; for example, the antiretroviral drug didanosine, although no longer in clinical use, enhances neuronal injury during FIV infection (31). Regardless of the initiating mechanism, therapies that promote neuronal recovery and repair remain important once nerve damage has developed.

Beyond mechanism-specific interventions, the involvement of TRPV1 and TRPA1 across distinct viral models suggests that shared downstream ion channels may provide therapeutic targets despite differences in initiating mechanisms. TRPV1 and TRPA1 antagonists could in principle attenuate nociceptor sensitization driven by viral and immune factors. Notably, voltage-gated sodium channels (NaVs) have not been systematically investigated in the context of virally initiated pain, although herpes simplex virus-1 infection and latency have been demonstrated to alter NaV expression and function (65–67). Suzetrigine, a NaV1.8 inhibitor approved for moderate to severe acute pain in adults (68), warrants investigation as a potential treatment for virally initiated pain states.

Some candidate targets already have compounds developed for other indications that could be repurposed. TNF-alpha and IL-1beta biologics are approved for autoimmune and autoinflammatory conditions (69, 70), and TRPV1-targeted high-concentration capsaicin formulations are approved for neuropathic pain, including post-herpetic neuralgia (71). Prevention remains an effective means of avoiding virally initiated pain altogether, with vaccines already in routine veterinary use for several of the viruses discussed here (72). In current clinical and veterinary practice, symptomatic analgesic management remains the standard of care and will continue to be necessary until mechanistic therapies are validated and available.

Considerable work remains to define the mechanisms underlying virally initiated pain across viral families and animal species. Optimal treatment strategies will likely be multifactorial and depend on viral biology, disease stage, and host factors. Continued collaboration among veterinarians, virologists, immunologists, and pain neuroscientists will be essential for translating mechanistic insight into more effective therapies for both human and veterinary patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

SD: Conceptualization, Visualization, Writing – original draft, Writing – review & editing.

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