REVIEW ARTICLE

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Integrated stress response and postoperative neuroinflammation in veterinary surgery: therapeutic perspectives

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Postoperative inflammation and pain remain major challenges in veterinary surgery, significantly affecting tissue healing, recovery time, and overall patient welfare. Surgical trauma activates a complex physiological response involving neuroendocrine stimulation, inflammatory mediator release, oxidative stress, and immune dysregulation. Central to these processes is the Integrated Stress Response (ISR), a highly conserved intracellular signaling pathway that regulates cellular adaptation during physiological stress. Activation of ISR-associated pathways, particularly PERK-eIF2?-ATF4 signaling, initially promotes cellular survival and restoration of proteostasis; however, prolonged activation may contribute to apoptosis, neuroinflammation, delayed healing, and chronic pain sensitization. Current perioperative management in veterinary medicine primarily relies on multimodal analgesic protocols including NSAIDs, opioids, alpha-2 adrenergic agonists, NMDA receptor antagonists, and local anaesthetics. Although these therapies effectively reduce nociceptive signaling and inflammation, they are often associated with adverse effects such as gastrointestinal toxicity, renal injury, immunosuppression, and delayed tissue repair. Consequently, recent research has increasingly focused on targeted pharmacological approaches that modulate upstream cellular stress pathways and inflammatory signaling networks. Emerging therapies such as ISR modulators, antioxidant compounds, anti-cytokine strategies, and immunomodulatory agents show promise in reducing oxidative injury, preserving cellular homeostasis, and improving periopera-tive outcomes. Advances in precision perioperative medicine, including biomarker-guided analgesia, opioid-sparing anaesthesia, and species-specific multimodal protocols, may further enhance recovery and minimize postoperative complications in veterinary patients. Understanding the molecular interactions between surgical stress, neuroinflammation, and ISR activation could provide novel therapeutic targets for improving pain management, accelerating wound healing, and optimizing welfare across diverse veterinary species.

Keywords: Integrated Stress Response (ISR), Multimodal analgesia, Oxidative stress, Postoperative inflammation, Veterinary surgery

Surgical trauma in veterinary medicine triggers a highly coordinated and complex physiological cascade that rapidly activates localized and systemic inflammatory pathways (Hernández-Avalos *et al.*, 2021). This tissue disruption prompts the immediate release of a plethora of chemical mediators, including vasoactive amines, cytokines, and prostaglandins, which alter the local microvascular and cellular environment (Desborough, 2000). The magnitude of this inflammatory activation is directly proportional to the invasiveness of the surgical technique, the extent of tissue dissection, and the duration of operative trauma (Lloyd, 2017). Uncontrolled perioperative stress resulting from surgical trauma profoundly delays wound healing, disrupts protein synthesis, and impairs overall tissue recovery (Hekman *et al.*, 2014). These neuroendocrine and metabolic adaptations lead to hypermetabolism, skeletal muscle catabolism, and a temporary state of immunosuppression that increases the risk of postoperative infection (Desborough, 2000). Consequently, managing postoperative pain and systemic inflammation remains a major concern for veterinary clinicians seeking to preserve patient welfare.

Severe, unmanaged acute pain not only causes substantial suffering but also triggers maladaptive behavioural changes such as anorexia, hiding, and self-mutilation, which further delay recovery. Traditional veterinary analgesic protocols have historically focused on symptomatic relief through suppression of peripheral nociceptive signaling pathways. Although standard therapies such as NSAIDs and opioids are highly effective, they are associated with significant adverse effects, particularly in geriatric, hypotensive, or metabolically compromised animals. To overcome these limitations, increasing attention has been directed toward intracellular stress pathways and precision periopera-tive care models. Minimizing surgical stress response through advanced anaesthetic techniques, regional blockade, and molecular interventions is essential for optimizing outcomes in critically ill patients. In this context, understanding the molecular mechanisms of the Integrated Stress Response (ISR) may provide novel and highly specific therapeutic targets for veterinary surgery. By selectively modulating conserved signaling pathways involved in cellular proteostasis, clinicians may protect vital organs from ischemic, metabolic, and inflammatory injury (Costa-Mattioli and Walter, 2020).

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This review aims to bridge the gap between systemic surgical stress and cellular adaptive networks, thereby providing a framework for future pharmacological interventions in veterinary patients.

Surgical stress response in animals

Neuroendocrine response to surgery

The neuroendocrine response to surgical trauma represents a protective, although potentially harmful, evolutionary mechanism triggered by noxious stimuli. Following surgical incision, afferent neural impulses travel from peripheral nociceptors to the spinal cord and ascending pathways of the hypothalamus, initiating a systemic neurohormonal cascade (Hekman *et al.*, 2014). This central activation stimulates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in rapid release of adrenocorticotropic hormone (ACTH) into the bloodstream. In response to ACTH, the adrenal cortex synthesizes and secretes large quantities of cortisol into systemic circulation. Elevated perioperative cortisol concentrations are widely recognized as important biomarkers of acute physiological and psychological stress in veterinary medicine (Hekman *et al.*, 2012). Cortisol acts as a major catabolic hormone, mobilizing energy reserves to sustain high-demand organs such as the brain during periods of physiological stress (Tippairote *et al.*, 2025). This hormonal surge promotes hepatic gluconeogenesis and glycogenolysis, leading to transient hyperglycemia that may be exacerbated by insulin resistance. In the liver, glucocorticoids enhance the activity of hepatic glutamic-pyruvic transaminase, accelerating the transamination of skeletal muscle-derived alanine into pyruvate. Simultaneously, surgical stress activates the sympathetic nervous system, resulting in rapid release of catecholamines, particularly epinephrine and norepinephrine, from the adrenal medulla and sympathetic nerve endings. These catecholamines increase systemic blood pressure, elevate heart rate, and enhance myocardial contractility to optimize peripheral oxygen delivery (Cusack and Buggy, 2020). In combination with cortisol, catecholamines stimulate lipid metabolism by converting triglycerides into glycerol and free fatty acids, thereby providing substrates for ketogenesis (Rahimi and Gupta, 2025).

Inflammatory cascade following surgery

The cellular damage associated with veterinary surgery initiates localized and systemic inflammatory cascades mediated by specialized immune cells. Leukocytes, fibroblasts, and endothelial cells at the injury site synthesize and release low-molecular-weight proteins known as pro-inflammatory cytokines. Interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) are the primary mediators initiating the systemic acute-phase response. IL-1 exists in two isoforms, with IL-1β acting as an endogenous pyrogen that stimulates hypothalamic prostaglandin E2 production, thereby inducing postoperative fever and anorexia. TNF-α acts synergistically with IL-1 to accelerate skeletal muscle proteolysis, leading to rapid muscle wasting and cachexia in severely stressed surgical patients. Additionally, prolonged exposure to excessive concentrations of IL-1 and TNF-α exerts negative inotropic effects on the myocardium and promotes profound vasodilation through nitric oxide upregulation. Unlike other cytokines, plasma IL-6 concentrations increase proportionally with the magnitude of tissue trauma, making IL-6 a reliable biomarker of surgical invasiveness.

These circulating cytokines stimulate the arachidonic acid cascade, leading to upregulation of cyclooxygenase (COX) enzymes. While the constitutively expressed COX-1 isoform mediates essential homeostatic functions such as gastrointestinal mucosal protection, platelet hemostasis, and renal perfusion, the inducible COX-2 isoform is rapidly upregulated in response to tissue injury. COX-2 converts arachidonic acid into pro-inflammatory prostaglandin E2, which sensitizes peripheral nociceptors and intensifies hyperalgesia (Gugliandolo *et al.*, 2020). The localized inflammatory microenvironment is further complicated by the generation of reactive oxygen and nitrogen species (ROS/RNS), leading to severe oxidative stress. These highly reactive free radicals attack cellular membrane lipids, generating toxic peroxidation products such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). Oxidative stress activates key intracellular transcription factors, including nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), which further upregulate COX-2 and cytokine expression. In articular cartilage, this oxidative and cytokine-rich microenvironment induces telomere instability, chondrocyte senescence, and cartilage degradation, thereby contributing to osteoarthritis in dogs. Administration of potent antioxidants such as N-acetylcysteine (NAC) or vitamin C may restore intracellular glutathione (GSH) levels and protect joint tissues from oxidative injury (Dycus *et al.*, 2013).

Species variations

Different veterinary species exhibit marked variations in their physiological and behavioural responses to surgical stress, necessitating species-specific anaesthetic and perioperative management protocols (Table 1). In dogs, postoperative stress commonly manifests as depression, anxious behaviour, excessive site licking, and the characteristic "prayer posture," with salivary cortisol serving as an important biomarker of stress (Hekman *et al.*, 2012). Laparoscopic procedures in dogs produce milder inflammatory and oxidative stress responses compared with open surgeries, as evidenced by lower postoperative myeloperoxidase (MPO) and

Table 1: Species-specific biomarkers, and physiological risks, associated with surgical stress in animals.

Species	Primary biomarkers of surgical stress	Pathophysiological risks
Dog	Salivary/plasma cortisol, stress leukogram, glycemic levels, urinary serotonin	Ventricular dysrhythmias, systemic oxidative stress, tissue transamination
Cat	Blood glucose, high-sensitivity cardiac troponin I (hs-cTnI), serum amyloid A (SAA)	Transient myocardial thickening (TMT), hypercoagulability
Horse	Plasma cortisol, serum amyloid A (SAA), blood lactate, depletion of muscle ATP and creatine phosphate (CP)	Ventilation-perfusion (V/Q) mismatch, alveolar collapse, post-anaesthetic colic, reduced ACS cytokine quality
Cattle	Plasma cortisol, Substance P (SP), haptoglobin, fibrinogen	Tympany during recumbency, prolonged distress following dehorning or disbudding

malondialdehyde (MDA) concentrations. Cats are highly stress-sensitive and often exhibit subtle pain-associated behaviours such as hiding, rigid posture, and hyporexia (Hernández-Avalos *et al.*, 2019). Surgical stress in cats may also induce hyperglycemia, transient myocardial thickening, and hypercoagulability, requiring careful perioperative monitoring (Takano *et al.*, 2022)

Molecular mechanisms of the integrated stress response

The ISR is a highly conserved intracellular signaling pathway that regulates cellular metabolism and proteostasis during stress conditions. Central to the ISR is phosphorylation of eukaryotic translation initiation factor 2 alpha (eIF2α), which suppresses global protein synthesis while selectively promoting translation of stress-responsive genes such as activating transcription factor 4. Under stressful conditions, phosphorylated eIF2α inhibits eIF2B activity, thereby reducing cellular energy expenditure and limiting synthesis of damaged proteins.

Four major kinases regulate ISR activation in response to distinct stressors (Table 2). PKR-like endoplasmic reticulum kinase (PERK) responds to endoplasmic reticulum stress, general control non-derepressible 2 (GCN2) is activated by amino acid deprivation, double-stranded RNA-dependent protein kinase (PKR) responds to viral and ribotoxic stress, and heme-regulated inhibitor kinase (HRI) is activated during oxidative stress and heme deficiency (Rodrigues *et al.*, 2018). Activation of these pathways promotes adaptive cellular responses, including autophagy, antioxidant defense, and molecular chaperone synthesis through ATF4-mediated transcriptional regulation.

Pain and neuroinflammation in postoperative animals

Surgical procedures in veterinary patients activate neuroinflammatory and endocrine responses that contribute to hyperglycemia, delayed wound healing, and transition from physiological to pathological pain. Effective management of postoperative pain therefore requires pre-emptive multimodal analgesia (MMA), which combines agents acting at different levels of the neuraxis to maximize analgesia while minimizing adverse effects (Bhatia and Buvanendran, 2019). Common veterinary MMA protocols include NSAIDs, opioids, local anaesthetics, and NMDA receptor antagonists. NSAIDs reduce prostaglandin synthesis through cyclooxygenase (COX) inhibition, whereas opioids such as buprenorphine, fentanyl, and tramadol provide central analgesia for moderate to severe pain (Monteiro and Simon, 2022). Local anaesthetics including lidocaine and bupivacaine inhibit peripheral nerve conduction by blocking sodium channels, while ketamine and magnesium sulfate reduce central sensitization through NMDA receptor antagonism (Mehta, 2020).

Peripheral sensitization

Peripheral sensitization occurs when inflammatory mediators lower the activation threshold of primary afferent nociceptors, resulting in exaggerated pain responses. Surgical tissue injury releases an "inflammatory soup" containing prostaglandins, bradykinin, ATP, histamine, serotonin, nerve growth factor, and pro-inflammatory cytokines such as TNF-α, which collectively enhance nociceptor excitability. The transient receptor potential vanilloid 1 (TRPV1) channel plays a major role in amplifying inflammatory pain signaling through sensitization of C fibers and Aδ fibers (Amaya-Rodriguez *et al.*, 2024). Experimental therapies targeting TRPV1 channels, including resiniferatoxin and selective antagonists, have shown promise in reducing inflammatory pain and peripheral hypersensitivity (Aghazadeh *et al.*, 2017).

Central sensitization

Central sensitization is characterized by increased excitability of dorsal horn neurons following repetitive nociceptive stimulation. Persistent activation of NMDA receptors removes the voltage-dependent magnesium block, allowing calcium influx and promoting long-term potentiation of pain pathways (Zhuo, 2009). This process results in hyperalgesia and allodynia, where normally non-painful stimuli become painful. Astrocytic dysfunc-tion and reduced glutamate clearance through downregulation of excitatory amino acid transporter 2 (EAAT2) further

Table 2: Major ISR Kinases, their activating stimuli, sensor mechanisms, and physiological functions in cellular stress adaptation.

ISR Kinase	Primary inducer	Sensor Domain mechanism	Physiological outcome
PERK	Accumulation of unfolded or misfolded proteins in the endoplasmic reticulum (ER)	Transmembrane ER luminal stress-sensing domain	Promotes ATF4 translation and induces CHOP-mediated apoptosis during prolonged ER stress
GCN2	Amino acid starvation and glucose deprivation	Histidyl-tRNA synthetase-like regulatory domain	Regulates histone lactylation and upregulates amino acid synthesis genes, including asparagine synthesis pathways
PKR	Double-stranded RNA (dsRNA) and viral infection	Double-stranded RNA-binding domains	Inhibits viral replication and promotes stress granule formation
HRI	Heme deficiency, iron depletion, and oxidative stress	Heme-binding autoregulatory domain	Suppresses hemoglobin translation and protects cells from oxidative and ischemic injury

sustain central sensitization and chronic pain states (Wang *et al.*, 2025).

Cytokines and pain pathways

Surgical trauma and nerve injury trigger neuroimm-une responses mediated by pro-inflammat-ory cytokines such as IL-1β, TNF-α, and IL-6, which play critical roles in postoperative pain and central sensitization (Silva *et al.*, 2024). TNF-α acts as an early inflammatory mediator that enhances glutamate release and potentiates AMPA and NMDA receptor activity, thereby amplifying neuronal excitability and pain hypersensitivity (Olmos and Lladó, 2014). IL-6 primarily contributes to pathological pain through suppression of inhibitory synaptic transmission and activation of trans-signaling pathways associated with thermal hyperalgesia (Zhou *et al.*, 2016).

Oxidative stress and pain amplification

Surgical trauma and tissue injury generate reactive oxygen species (ROS), leading to oxidative stress and cellular damage in animals. Excessive ROS production during procedures such as laparotomy and laparoscopy contributes to lipid peroxidation, depletion of antioxidant reserves, and increased postoperative inflammatory responses, as indicated by elevated malondialdehyde (MDA) concentrations and reduced total antioxidant capacity (Lv et al., 2025). Open surgical procedures generally produce greater oxidative stress and inflammatory injury compared with minimally invasive techniques. Oxidative stress also amplifies pain pathways through activation of transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid 1 (TRPV1) channels on nociceptive neurons (Carrasco *et al.*, 2018). ROS accumulation within dorsal root ganglia and spinal dorsal horn neurons enhances glutamatergic transmission, promotes hyperalgesia, and sustains central sensitization. Furthermore, ROS-induced activation of microglial pathways increases production of pro-inflammatory mediators and establishes a feed-forward neuroinflammatory cycle that perpetuates postoperative pain. Antioxidant therapies and ROS scavengers have therefore emerged as promising strategies for reducing oxidative injury, neuroinflammation, and pain amplification in veterinary perioperative care. The proposed interac-tion between surgical trauma, oxidative stress, ISR activation, neuroinflammation, and postoperative complications is summarized in figure 1.

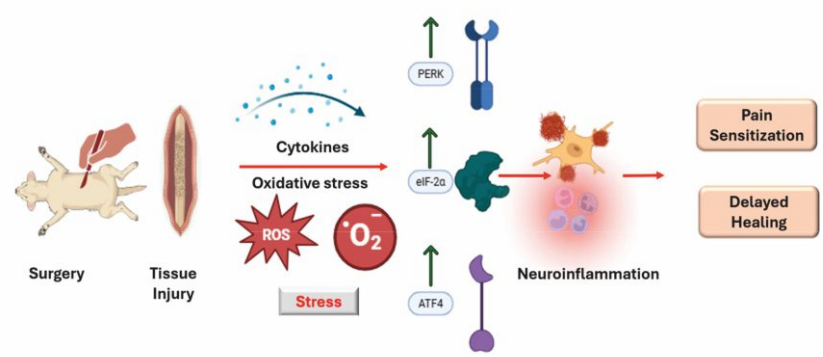

Fig. 1: Proposed relationship between surgical trauma, ISR activation and postoperative neuroinflammation.

Current pharmacological interventions

Postoperative pain and inflammation in veterinary patients are managed using a multimodal pharmacological approach targeting both peripheral and central nociceptive pathways. Commonly employed therapeutic agents include NSAIDs, opioids, alpha-2 adrenergic agonists, NMDA receptor antagonists, and local anaesthetics. These drugs not only reduce pain perception but also help attenuate inflammatory responses, decrease stress-associated neuroendocrine activation, and improve post-surgical recovery. Despite their clinical effectiveness, many conventional analgesics are associated with adverse effects and primarily target downstream inflammatory mediators rather than the underlying cellular stress pathways involved in surgical injury.

NSAIDs

NSAIDs exert their anti-inflammatory and analgesic effects primarily through inhibition of COX enzymes, thereby reducing the conversion of arachidonic acid into prostaglandins. Prostaglandins are important inflammatory mediators responsible for vasodilation, increased vascular permeability, pain sensitization, redness, heat, and tissue oedema following surgical injury. By suppressing prostaglandin synthesis, NSAIDs effectively reduce inflammation, swelling, and postoperative pain. However, despite their clinical benefits, NSAIDs must be used cautiously due to potential adverse effects such as gastrointestinal ulceration, nephrotoxicity, postoperative bleeding, and possible delays in bone and tissue healing. NSAIDs may cause renal toxicity by reducing renal blood flow, particularly in patients experiencing dehydration, hypotension, or shock. Gastrointestinal toxicity is another major concern associated with NSAID therapy. Non-selective NSAIDs inhibit COX-1 activity, leading to decreased prostaglandin production and reduced mucus secretion, thereby increasing susceptibility of the gastric mucosa to acid-induced injury (Wallace, 2008). Consequently, adverse effects such as vomiting, diarrhoea, gastric irritation, and ulceration may occur. In addition, excessive suppression of the inflammatory response may interfere with normal tissue repair processes and contribute to delayed healing and recovery following surgery.

Opioids

Opioids are centrally acting analgesic agents widely used for the management of moderate to severe postoperative pain in veterinary patients. These drugs act primarily on opioid receptors within the central nervous system to reduce pain perception and alter nociceptive transmission. Commonly used opioids include morphine, tramadol, and butorphanol. In addition to analgesia, opioids may produce several physical and psychological effects such as sedation, drowsiness, mental confusion, nausea, constipation, euphoria, and in some cases, hyperactivity (Benyamin *et al.*, 2008). Opioids are commonly incorporated into multimodal analgesic protocols, in which two or more systemic analgesics are combined with regional anaesthetic techniques for effective perioperative pain management. Multimodal analgesia aims to enhance analgesic efficacy while reducing opioid requirements and minimizing opioid-associated adverse effects through the combined use of non-opioid analgesics acting via different mechanisms.

Alpha-2 agonists

Alpha-2 adrenergic agonists are commonly used in veterinary anaesthesia for their sedative, anxiolytic, analgesic, and stress-reducing properties. These agents produce central nervous system depression, making them valuable pre-anaesthetic medications in perioperative management. In addition to inducing sedation and reducing anxiety, alpha-2 agonists enhance the effects of other anaesthetic agents and decrease overall anaesthetic requirements during surgery. They also provide significant analgesic effects at both spinal and supraspinal levels. The pharmacological effects of alpha-2 agonists are mediated through binding to presynaptic alpha-2 adrenergic receptors on sympathetic nerve terminals, resulting in inhibition of norepinephrine release and reduced sympathetic outflow (Smith and Elliott, 2001). Consequently, these drugs produce sedation, analgesia, bradycardia, hypotension, and muscle relaxation. Commonly used alpha-2 agonists in veterinary medicine include xylazine, dexmedetomidine, and medetomidine.

NMDA receptor antagonists

Ketamine hydrochloride is a widely used injectable dissociative anaesthetic agent employed for short-term anaesthesia and analgesia in both human and veterinary medicine. Ketamine acts primarily as a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. Activation of NMDA receptors by the excitatory neurotransmitter glutamate plays a critical role in the development of central sensitization, a condition characterized by increased responsiveness of the central nervous system to normal sensory stimuli, resulting in exaggerated pain perception and hypersensitivity (Mion and Villevieille, 2013). In perioperative veterinary medicine, ketamine is commonly incorporated into multimodal anaesthetic protocols to reduce spinal cord hyperexcitability and prevent amplification of nociceptive signaling. NMDA receptor antagonists, along with opioids and alpha-2 agonists, help attenuate central sensitization and improve postoperative pain management by limiting excessive neuronal excitation within the spinal cord.

Local anaesthetics

Local anaesthetics are important components of multimodal perioperative analgesia in veterinary medicine (Margeti *et al.*, 2024). Lidocaine, one of the most commonly used local anaesthetic agents, exerts its effects by blocking voltage-gated sodium channels

in peripheral nerves, thereby preventing initiation and conduction of nerve impulses. In addition, lidocaine inhibits neurons involved in visceral pain transmission, contributing to its analgesic efficacy. Constant rate infusion (CRI) of lidocaine has gained considerable importance in veterinary anaesthesia due to its analgesic, anti-inflammatory, and anaesthetic-sparing effects. In an experimental study involving dogs undergoing intraocular surgery, intraoperative lidocaine infusion provided analgesic effects comparable to morphine without causing clinically significant alterations in blood pressure or heart rate during isoflurane anaesthesia (Ortega and Cruz, 2011). Furthermore, studies have demonstrated that lidocaine CRI produces minimal adverse effects while providing analgesic efficacy comparable to agents such as morphine, amitriptyline, and gabapentin used in pain management (Ortega and Cruz, 2011).

Lidocaine is also widely utilized in various regional anaesthetic techniques. Peripheral nerve blocks involve administration of lidocaine near specific nerves, such as the brachial plexus or femoral nerve, to provide localized analgesia during limb surgeries. Central neuraxial blocks, including epidural and spinal anaesthesia, are used to desensitize larger anatomical regions such as the lower abdomen and hind limbs. In addition, intravenous regional anaesthesia (Bier's block) involves intravenous administration of lidocaine while a tourniquet isolates the limb, allowing short-term regional analgesia for distal limb procedures (Mendez-Angulo *et al*., 2020).

Although current pharmacological interventions effectively control postoperative pain and inflammation, many therapies are associated with adverse effects and primarily target downstream inflammatory mediators and nociceptive pathways. Consequently, recent research has focused on novel therapeutic strategies targeting cellular stress pathways, neuroinflammation, and immune modulation to improve perioperative outcomes in veterinary patients.

Emerging pharmacological targets

Recent advances in perioperative medicine have emphasized the importance of targeting cellular stress pathways, neuroinflammation, and oxidative stress in addition to conventional analgesic therapies. The dual role of the ISR as both a protective adaptive mechanism and a potential driver of apoptosis has made it an important target for emerging pharmacological interventions in veterinary surgery. Small-molecule modulators such as the Integrated Stress Response Inhibitor (ISRIB) and eIF2B activator 2BAct regulate eIF2α signaling and preserve cellular proteostasis during acute stress conditions. ISRIB stabilizes the active eIF2B complex, thereby preventing maladaptive ISR activation and reducing CHOP-mediated apoptosis. Conversely, salubrinal prolongs protective eIF2α phosphorylation by inhibiting the GADD34/PP1 phosphatase complex during severe cellular stress (Hicks *et al.*, 2023).

Beyond direct ISR modulation, combined anti-inflammatory and antioxidant therapies may provide synergistic perioperative benefits. Co-administration of the selective COX-2 inhibitor firocoxib with vitamin C reduces oxidative stress, suppresses prostaglandin E_2 (PGE_2) production, and attenuates nuclear factor-kappa B (NF-κB)-mediated inflammatory pathways during ischemia-reperfusion injury (Gugliandolo et al., 2020). In regenerative veterinary medicine, autologous conditioned serum (ACS) has emerged as a promising biological therapy for reducing synovitis and protecting articular cartilage through elevated concentrations of IL-1 receptor antagonist (IL-1Ra), interleukin-10 (IL-10), and insulin-like growth factor-1 (IGF-1) (Ortved, 2023). Integration of these targeted therapies with locoregional anaesthesia represents an important advancement toward precision perioperative care. By preserving cellular homeostasis and attenuating systemic inflammatory responses, these emerging strategies may reduce postoperative morbidity, accelerate tissue healing, and improve recovery outcomes in veterinary patients (Hekman *et al.*, 2014).

ISR modulators

ISR is an adaptive cellular pathway activated during conditions such as endoplasmic reticulum stress, oxidative stress, hypoxia, and tissue injury (Costa-Mattioli and Walter, 2020). Activation of the PERK pathway leads to phosphorylation of eIF2α, resulting in reduced global protein synthesis and selective activation of stress-response genes such as activating transcription factor-4 (ATF4) and C/EBP homologous protein (CHOP) (Rozpedek *et al.*, 2016). Although ISR activation initially promotes cellular survival and restoration of homeostasis, prolonged activation may contribute to inflammation, apoptosis, and delayed tissue healing. Experimental compounds targeting PERK and eIF2α signaling are being investigated for their potential to reduce neuroinflammation and improve postoperative outcomes (Zeng *et al.*, 2025).

Anti-cytokine strategies

Excessive production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) plays an important role in postoperative inflammation, pain sensitization, and tissue injury (Wen *et al.*, 2011). Anti-cytokine strategies aim to reduce excessive inflammatory responses by inhibiting specific cytokines or their signaling pathways (Venkatesha *et al.*, 2014). Experimental approaches including monoclonal antibodies, soluble cytokine receptors, and IL-1 receptor antagonists have shown potential in modulating inflammatory reactions and reducing tissue damage. However, excessive cytokine suppression may impair host defense mechanisms and delay normal healing processes (Efron *et al*., 2004).

Antioxidants

Oxidative stress resulting from excessive production of reactive oxygen species (ROS) contributes significantly to post-surgical inflammat-ion and cellular injury. Antioxidants such as melatonin and N-acetylcysteine (NAC) have gained attention for their anti-inflammatory and cytoprotective properties (Tenório *et al.*, 2021). Melatonin acts as a potent free radical scavenger and enhances endogenous antioxidant enzyme activity while also exhibiting neuroprotective and immunomodulatory effects. NAC functions primarily as a precursor of glutathione and helps reduce oxidative stress, neuroinflammation, and mitochondrial dysfunction (Raghu *et al.*, 2021).

Immunomodulatory hormones

Immunomodulatory hormones such as progesterone, glucocorticoids, and cannabinoid-related compounds are emerging as potential therapeutic targets for controlling inflammation and immune dysregulation. Progesterone exhibits anti-inflammatory effects through modulation of nuclear factor-kappa B (NF-κB) signaling pathways and may help reduce excessive inflammatory responses. Glucocorticoids remain important anti-inflammatory agents in perioperative medicine due to their ability to suppress cytokine production and immune activation; however, prolonged use may impair wound healing and increase susceptibility to infection. Cannabinoid pathways, particularly CB2 receptor signaling, have also gained attention because of their analgesic, anti-inflammatory, and neuroprotective properties. Selective targeting of these pathways may provide future opioid-sparing and precision-based therapeutic approaches in veterinary perioperative care. Further translational and species-specific studies are required to evaluate the safety, efficacy, and clinical applicability of these emerging therapies in animals.

Limitations, translational challenges and species-specific applicability

Despite growing interest in the role of the Integrated Stress Response (ISR) in inflammation and tissue injury, current evidence supporting its application in veterinary surgery remains limited. Most mechanistic studies investigating PERK-eIF2α-ATF4 signaling, neuroinflammation, and ISR-targeted interventions have been conducted in rodent models, cell cultures, or human biomedical research, making direct extrapolation to veterinary species challenging. Furthermore, the majority of available studies focus on molecular and biochemical biomarkers rather than clinically relevant surgical outcomes such as postoperative pain scores, wound healing rates, duration of hospitalization, and long-term recovery. Although ISR modulators such as ISRIB and salubrinal have demonstrated promising anti-inflammatory and cytoprotective effects in experimental settings, their pharmacokinetics, safety profiles, species-specific dosing regimens, and long-term adverse effects remain largely undefined in domestic animals. Excessive suppression of ISR pathways may also interfere with essential adaptive cellular responses involved in tissue repair, immune competence, and maintenance of cellular homeostasis. Similar limitations exist for emerging anti-cytokine therapies, including monoclonal antibodies and cytokine receptor antagonists, which may compromise host defense mechanisms, increase susceptibility to opportunistic infections, impair normal wound healing, and potentially disrupt beneficial inflammatory processes necessary for recovery. In addition, the high cost, limited availability, regulatory constraints, and withdrawal period requirements associated with biological therapeutics may restrict their practical application, particularly in food-producing animals. Veterinary species differ considerably in their physiological responses to surgical stress, inflammatory mediator production, pain perception, metabolic regulation, and pharmacological sensitivity, which may significantly influence ISR activation and therapeutic efficacy. Variations in hepatic metabolism, receptor expression, immune regulation, and drug disposition among dogs, cats, horses, and cattle further emphasize the need for species-specific investigations. Therefore, future research should prioritize controlled clinical trials and translational studies aimed at validating ISR-associated biomarkers, evaluating the safety and efficacy of ISR-targeted therapies, and developing evidence-based perioperative protocols tailored to individual veterinary species.

Conclusions

Surgical trauma in veterinary patients initiates a complex physiological response involving neuroendocrine activation, inflammatory cascades, oxidative stress, and intracellular stress-signaling pathways. Release of cortisol, catecholamines, and pro-inflammatory mediators following tissue injury contributes to hypermetabolism, tissue catabolism, immune dysregulation, and delayed healing. Under these conditions, the Integrated Stress Response (ISR) functions as a critical regulator of cellular adaptation by balancing protective stress responses with apoptosis depending on the severity and duration of perioperative stress. Although conventional analgesics effectively control postoperative pain and inflammation, they primarily target downstream nociceptive pathways and may not adequately address the underlying molecular mechanisms associated with surgical stress and tissue injury. Emerging pharmacological approaches, including ISR modulators, antioxidant therapies, anti-cytokine strategies, and immunomodulatory agents, represent promising advances in precision perioperative medicine. By preserving cellular proteostasis, reducing oxidative injury, and attenuating maladaptive inflammatory signaling, these therapies may

improve recovery, minimize postoperative complications, and enhance patient welfare. Future veterinary research should focus on translational and species-specific clinical studies to evaluate the safety and efficacy of these novel interventions. A deeper understanding of the molecular interactions between systemic stress responses and intracellular adaptive pathways may ultimately lead to improved pain management and optimized surgical outcomes across diverse veterinary species.

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