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Overview

Defining and Managing Pain in Stroke and Traumatic Brain Injury Research

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Neurologic conditions such as stroke and traumatic brain injury are challenging conditions to study in humans. Animal models are necessary to uncover disease processes and develop novel therapies. When attempting to model these or other neurologic diseases, the accompanying anesthesia and analgesia create variables that are not part of the onset of the clinical disease in the human population but are critical components of the postinjury care both in humans and animals. To maximize model validity, researchers must consider whether the disease process or a novel therapy is being studied. Damage to the neurons of the brain or the spinal cord is not painful at the neural tissue itself, but alterations to nociceptive signaling along the pain pathway can induce chronic pain. In addition, trauma or surgery leading to the event is associated with damage to peripheral tissue. Inflammation is inextricably associated with tissue injury. Inflammation is known to evoke nociception in the periphery and drive long-term changes to neurons in the CNS. Analgesics and anesthetics alter these responses yet are required as part of humane animal care. Careful planning for effective drug administration consistent with the standard of care for humans and equivalent animal care is required.

Abbreviation: TBI, traumatic brain injury

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Like other organs or tissues in the body, the nervous system is subject to injury and disease. Neurologic conditions that most commonly lead to referrals for rehabilitation and physical therapy include both stroke and traumatic brain injury (TBI), as well as other neurologic conditions.[55] The estimate of global disease burden of neurologic conditions ranks stroke as one of the largest contributors to death and disability in persons older than 5 y.[27]

To make valid decisions regarding appropriate therapeutic care for animals that are part of stroke or TBI research projects, researchers and laboratory animal veterinarians need information regarding the treatment and therapy of human patients with these types of conditions.

The complexity of the nervous system and the fact that it drives perception and behavior create challenges for those who would examine neurologic changes responsible for disease and develop novel methods of treating the disease process. The in vitro setting currently falls short in its ability to model complex tissues, circulation of blood and lymph, and changes in whole-organism behaviors, so it is necessary to screen novel therapeutics within whole-animal models before assessing candidate therapies in humans. Such work must be carried out humanely and ethically, with all possible care toward minimizing pain and suffering. Because these models involve the creation of an injury to the animal, appropriate analgesics and anesthetics should be considered for incorporation into the research plan, or their omission must be carefully justified to bioethics committees, such as IACUC.

Neither stroke nor TBI is widely diagnosed as occurring spontaneously in the domestic animal or lab animal populations. Therefore, in vivo study of these conditions requires the creation of animal models. Spontaneous-onset models of hemorrhagic stroke do exist in gene- and diet-modified rodent strains but present significant difficulties in adjusting for time to onset and high variability between animals.[3] No animal model perfectly recapitulates a human disease condition, but each model has useful elements. To elucidate the insult to the CNS, stroke can be distinguished at the tissue level as either an occlusive or hemorrhagic event, whereas TBI may include both components. To grossly generalize the processes by which stroke and TBI cause damage to the brain, neuronal death is caused by diminished circulation (which can lead to hypoxia and buildup of cellular byproducts), inflammation during or after injury (for example reperfusion injury), or by physical damage to cells. The process of neuronal cell death has been described as occurring along at least 11 distinct pathways, and these cellular processes have been reviewed extensively.[23] Preclinical CNS injury research encompasses 2 general classes of research: mechanism and efficacy.[68] Mechanistic studies have as a goal the objective of determining the molecular processes that are associated with CNS injury and the negative sequelae that follow. Such studies help to identify opportunities for therapeutic intervention. It is important to ensure that preclinical experience recapitulates the human experience as closely as possible which may or may not include a therapeutic regimen. The goal of efficacy studies includes assessment of the effectiveness of a therapeutic intervention compared with no treatment (negative control) or standard-of-care treatment (positive control).

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In the context of animal models for stroke and TBI research, one publication[77] provides an overview of key inflammatory cells and mediators, time frame to neuroimmune activation and pain response, cellular and hormonal responses to pain, and a decision tree for evaluating analgesic use compared with withholding it. Additional reviews have focused on the selection of anesthetics[33,89] and analgesics.[89]

Aside from incidents arising during surgery, anesthesia is not typically a factor in the spontaneous occurrence of these common neurologic conditions in humans.[33] Conversely, anesthesia is nearly universally required for induction of direct injury to the CNS in animal models, excluding models where injury is incurred by minimally invasive means, for example in situations where the injurious substances (that is, chemotherapeutics, streptozotocin, drugs of abuse, and so forth) might be administered orally, by intraveneous injection or through self-administration.

Aspirin and other anticoagulant therapies are frequently administered to patients after acute ischemic stroke.[79] Prevention of reperfusion injury during the immediate poststroke period (3 to 4.5 h) is critical also.[67] Lastly, analgesic usage is the standard of care during stroke rehabilitation.[117] Consistent with current clinical management, a research plan might consider incorporating comparable analgesia and adjunctive medications to be a consistent model of clinical practice. However, such an approach may not be appropriate for every efficacy or mechanistic study. For example, analgesia and other supportive therapy may be precluded in studies assessing therapeutics that may have pharmacokinetic or dynamic interaction with analgesic or adjunctive medications. Furthermore, investigators seeking to define cellular mechanisms (mechanistic studies) may find that analgesic or adjunctive medications are neuroprotective, have neutral effects, or exacerbate injury. Stroke and TBI studies that systematically compare the effects of postoperative analgesic medications with no treatment are quite limited in number and have contradictory outcomes.

Each new research proposal must be evaluated individually, with consideration for specific objectives, the effects of the intervention and pain medication, and assessment of animal welfare issues. Robust evaluation requires a basic working knowledge of the experience of pain in human patients with these conditions as well as current therapy in these settings and the predicted likelihood of pain in preclinical models of stroke and brain injury. This review is intended to provide an overview of pain in the context of these conditions.

Neurologic Injury

Stroke and TBI are highly variable in the human population; the clinical impact of a stroke or TBI reflects the neurons that die as a result of the event.[75] The incidence of stroke rises with age;[6] rates of hospitalization and death from TBI are highest in the elderly population.[90]

Stroke. Approximately 7 million Americans older than 19 y self-report as having had a stroke. Overall stroke prevalence is estimated at 2.5%,[6] and ischemic stroke accounts for 87% of cases.[6] Stroke can be described broadly as an episode of overt or covert neurologic dysfunction arising from CNS injury that is caused by a vascular event that occurs in the absence of trauma.[93] The American Stroke Association defines 3 clinical categories of stroke: 1) infarcts secondary to ischemia (whether from thrombi, emboli, or global low blood pressure), 2) intracerebral hemorrhage, and 3) subarachnoid hemorrhage.[93] Due to the lack of nociceptors within neuronal tissues, these injuries do not cause pain within the brain, but 30% to 80% of patients with hemorrhage experience headache secondary to increased intracranial pressure from bleeding or occluded vascular drainage.[93] Acute headache onset is more commonly associated with hemorrhagic stroke, whereas a gradual progressive headache is associated with ischemic stroke.[75] Headache pain from stroke ranges in severity from mild to severe but is not associated with lesion size or location.[106] In addition, stroke injury leaves 1% to 10% of patients with chronic neuropathic pain, due to damage within the CNS spinothalamic pain pathways.[6] Furthermore, chronic musculoskeletal pain from spastically contracted muscles occurs in these populations and impairs return to daily function.[55]

TBI. Each year, approximately 2.8 million cases of TBI are diagnosed in the United States.[100] TBI can be defined formally as an alteration in brain function or other evidence of brain pathology that is caused by an external force;[64] TBI is literally a brain-rattling injury. The most common causes of TBI are falls, car accidents, and being struck by or against an object (in settings such as sports, assaults, and military activity).[100] Injury severity varies: a concussive blow to the head, chronic traumatic encephalopathy (repeated mild TBI), epidural or subdural hematomas, and a penetrating brain injury can all result in trauma to the brain.[25] In humans, pain arises from injuries caused by the event and frequently includes headache.[72] Similar to stroke injury, about 2/3[70] of TBI patients experience chronic pain, including chronic headache. An additional postinjury risk in this patient population is an increased likelihood of future ischemic stroke events.[9,49]

Immediate Concerns Regarding the Patient: Damage and Therapy

In ischemic stroke, neuronal damage is driven by hypoxic conditions caused by the ischemia.[114] Cerebral autoregulation is a reflex that increases cerebral blood flow around the ischemic zone.[33] As neuronal stores of ATP are exhausted in the ischemic area, excitotoxicity, oxidative stress, inflammation, autophagy, and apoptosis unfold, with depolarization of neuronal cell membranes because individual cells can no longer maintain transmembrane ion gradients.[33] These events can lead to spreading depolarization as more cells exhaust their ATP stores.[33]

In TBI, damage can be incurred[11] through direct contusion of brain, impacting or sliding against the interior of the skull (whether on the side of injury or on the contralateral side), shearing and stretching of brain tissue (axonal shearing), and the vascular response to the impact. The vascular response may include not only hemorrhage but also hematoma, increased intracranial pressure, decreased intracranial blood flow, and cerebral edema.[11] These alterations in cerebral blood flow lead to neuronal death marked by lipid peroxidation, intracerebral cytokine production, and increased COX2 protein expression.[25,89] Seizures may accompany the trauma.[89] Hemorrhagic stroke can be expected to display a similar progression in its vascular events.

Aspirin and targeted anticoagulants such as tissue plasminogen activator are commonly used in ischemic stroke patients.[79] An additional priority for TBI as well as ischemic stroke is thrombophylaxis, given that head trauma increases the risk of thromboembolic events (pulmonary emboli as well as secondary ischemic stroke).[44] Even blunt trauma to the cerebrovasculature (namely, cerebral or vertebral arteries) can be associated with ischemic stroke in as many as 65% of patients;[66] thus prophylactic antithrombotic agents are a critical part of clinical therapy. Reperfusion injury is another major concern; validated therapies used during the initial hours after injury include mild hypothermia in addition to minocycline, fingolimod, and other immunomodulatory agents.[67,89]

Acute-use medicinal therapies are not nearly as well defined for hemorrhagic stroke[48,91] as for ischemic stroke. When a patient with hemorrhagic stroke or TBI presents at a hospital emergency room, the clinician's priority is to forestall secondary tissue injury by preventing the immediate threats of systemic hypotension, hypoxia, and hypercarbia and by reducing the excess intracranial pressure.[112] In humans with hemorrhagic stroke or TBI, reducing intracranial pressure to levels at or below 20 mm Hg[34] is used as a proxy indicator for maintaining cerebral perfusion and oxygenation.[112]

As reported previously,[25] immediate care for TBI is highly variable depending on the severity of the injury but also revolves around clinical management of intracranial pressure. Immediate care to manage intracranial pressure is likely to include one of several methods, including elevating the head, inducing brief periods of hyperventilation in acute neurologic deterioration to induce vasoconstriction, and providing hyperosmolar therapy with mannitol to reduce blood viscosity and trigger autoregulation to cause transient vasoconstriction. Patients may be provided with prophylactic antiseizure medication and, to reduce demands on cerebral metabolism, they may be placed into therapeutic hypothermia or medically induced comas. The mildest cases of stroke or TBI may not even be recognized as an injury by the patient and thus are likely underrepresented in the patient population, whereas severe cases may involve procedures as invasive as bilateral decompressive craniectomies to relieve the mass effect (localized increase in pressure) caused by contusion or hematoma.

During patient rehabilitation after stroke, the most commonly used drugs[117] are acetaminophen, tramadol, opioids (for example, hydrocodone), NSAID (COX2 inhibitors), anticonvulsants (gabapentin), tricyclic antidepressants (amitriptyline), muscle relaxants (cyclobenzaprine), and antispasticity muscle relaxants (baclofen), while TBI drug therapy during rehabilitation varies.

In addition to the original insult to the neuronal tissue, a cascade of events driven by neuroinflammation leads to further cell death in the brain. Neuroinflammation is known to involve neurons, astrocytes, oligodendrocytes, pericytes, leukocytes, microglia, and a host of inflammatory mediators including chemokines, cytokines, nitric oxide, and others.[39,67]

Injury Grading Scales

For more than four decades, the acute severity of injury to the human brain has been measured according to the Glasgow Coma Scale,[83,101] which scores deficits in eye responses, motor responses, and verbal responses. More recently, scales supporting classification of stroke injury have been developed and include the National Institutes of Health Stroke Scale[2,7,28] or its shortened and modified form.[54] TBI is difficult to grade—agreement regarding a standard definition of mild TBI is particularly sparse[80]—but evaluation generally revolves around the duration of loss of consciousness, altered mental state, and posttraumatic amnesia.[73] The long-term outcomes from central neurologic injury—whether full recovery, various levels of disability, or death—are usually graded according to either the Glasgow Outcome Scale[40] or the modified Rankin Scale.[82,105]

All of these patient scoring systems more or less rely on the individual's ability to comprehend and respond to verbal communication. In contrast, postinjury scoring systems for animals focus on body movement or sensorimotor capabilities; examples validated in rodents[4] include the Garcia,[26] Modo,[68,69] and Longa[53] scales. To directly compare human patients and animal research models, as well as enhance reproducibility of prior work, it is arguably more useful to publish the targeted cerebral region, the force applied to the tissue, and the duration of force application than it is to attempt to map animal scoring systems against human patient scoring systems. The number of animals used and necessary duration of postinjury survival can be minimized through the thoughtful use of appropriate behavioral tests and serial assessments.[68]

Pain

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[65] Pain is a complex phenomenon and may be difficult to distinguish for selection of appropriate therapy. In addition, pain is usually a purposeful signal: it drives behavioral changes necessary to avoid impending or continuing tissue injury and informs the body where to direct healing efforts. However, not all pain is informative, particularly when it persists past tissue healing. It is important to note that psychologic factors that affect the likelihood of pain persistence, such as pain catastrophizing,[81,98] occur in humans and are not readily recapitulated in animal models.

Pain in human patients with a neurologic injury can be divided temporally, that is, acute or chronic. Acute pain generally lasts as long as the noxious stimulus persists or until tissue healing is complete. Such pain encompasses headache from nociceptors responding to dural stretching due to increased intracranial pressure (from hemorrhage or edema) as well as the pain due to the injury itself (in the case of trauma to the head or body). As a pain category, chronic pain is considered to be pain that persists beyond tissue healing, and it stems from a variety of causes. To provide appropriate pain therapy, the type and source of the pain must be considered carefully.

The International Association for the Study of Pain distinguishes[65] various types of pain sensation as well as 3 broad origins of pain. Multiple types of pain sensation and pain origin can be expected to occur as sequelae to neurologic injury. The categories pertinent to research into CNS injury are defined by the International Association for the Study of Pain as follows:

Types of pain sensation.

- *Nociception* is the neural process of encoding noxious stimuli. Note that this process does not necessarily culminate in a sensation of pain.
- *Allodynia* is pain from a stimulus that is not normally painful. A classic example in humans is the pain from touch on a sunburn.
- *Hyperalgesia* is increased pain from a stimulus that normally invokes pain.

Origins of pain.

- *Nociceptive pain* arises from actual or threatened damage to nonneural tissue due to activation of nociceptors (specialized peripheral neurons that encode noxious signals). Examples include pain arising from inflammation, damaged tissue, or hypoxic or ischemic conditions. This pain is acute and resolves with the cessation of the threat or healing of the tissue.
- *Neuropathic pain* is caused by a lesion to the somatosensory nervous system that constitutes the ascending (sensory) and descending (modulatory) pain pathways. In the brain, these areas include the thalamus, hypothalamus, periaqueductal gray, amygdala, sensory cortex, rostroventral medulla, and the tracts between them; in the spinal cord, tracts and regions associated with the pain pathway; and in the peripheral tissues, the soma, axons, and terminals of peripheral nociceptors. This chronic pain is due to damage to these crucial structures rather than an external insult; altered signaling in these structures may lead to pain sensation that persists beyond tissue healing.

- *Nociplastic pain* arises from altered nociception, despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain. This chronic pain is due to abnormal function of the pain pathway in the absence of a lesion, and its duration is not associated with tissue healing.

Behavioral signs indicating the presence of pain in an individual vary depending on species, strain, age, sex, and even social setting.[96] Although a particular model injury to the brain might be executed consistently, the outcome from the injury remains difficult to predict,[97] not unlike the highly heterogeneous outcomes observed in human patients with brain injuries. The important element to recognize is that—regardless of signalment and setting—the pain experience is multifaceted, and these diverse underlying origins need to be addressed with different therapeutics.

Pain Secondary to Model Induction

Central neurologic injury has been modeled in a wide variety[16,29,36] of laboratory animal species, not only the most widely used rodents[51] but even species as small as zebrafish.[17] Craniotomies in human patients frequently result in headache pain;[30] similar pain should be predicted in animals.

Typically, ischemic stroke is modeled with occlusive animal models,[10,46,97] some of which require craniotomy and others of which require only vascular access. The most widely used[13] ischemic stroke model involves *middle cerebral artery occlusion*, which is either permanent due to electrocoagulation or ligature via craniotomy,[86,99] or transient[13] through the introduction of emboli or filaments into the artery via intraarterial access. Hemorrhagic stroke can be modeled through either the *collagenase*[88,110] or *autologous whole-blood*[92,109] models, in which either substance is injected directly into the basal ganglia or other brain regions or peripherally through other intravenous access.[46,57,59] In addition, filaments can be introduced into the cerebral vasculature to create a perforating injury—the *monofilament perforation subarachnoid hemorrhage* model.[5] Acute, transient pain is associated with vascular access. Although headache may be difficult to discern in animals, it should be assumed to be present to the same extent in stroke models as in human patients.

Animal models of TBI are designed to create focal or generalized injury to the brain.[15,25,41,45,47,76,87,102] Some of these models include craniotomy, allowing direct access to the cerebral cortex to create the injury. The *fluid percussion injury* model[62,63] delivers a fluid pulse onto the exposed cerebral tissue; the *controlled cortical impact* model[19,50] is similar but involves a piston rather than fluid; likewise, the *penetrating injury* model[12,78,113] uses a projectile that is driven into the brain through a craniotomy. Transcutaneous (closed-skull) injuries created by pressure or force applied to the intact head may not require direct access to the neural tissue, but this process creates trauma not only to the brain but also damage to skin and skull. The *impact acceleration injury* model,[31,61,94] sometimes called specifically the *weight-drop injury* model,[21,60] does not require craniotomy; instead, a scalp incision may be used to provide access to cement a metal disc to the skull, thus allowing the dropped weight to create an acceleration injury without penetrating the skull. Unlike the majority of animal models of neurologic injury, the *blast* model[14,52,71,84] of TBI uses general trauma to the animal to generate the brain injury. These models, whether refined to create a mild or moderate brain injury, are capable of more fully recapitulating an important aspect of moderate to severe blast injury in humans, which is the associated shockwave and shrapnel with accompanying secondary tissue damage.[71]

To summarize, a primary and easily distinguished component of pain associated with stroke or TBI models is nociceptive pain, which can be expected to arise from headache as well as the surgical or traumatic process through which the injury is created.

Pain Due to Damage to Neural Tissue

Poststroke pain conditions are divided clinically into central poststroke pain, complex regional pain syndrome, and pain associated with muscle spasticity and shoulder subluxation.[104] These types of pain also can occur after TBI, depending on the location of injury. Neuropathic pain from damage to neural structures that are associated with the processing of pain is widely recognized and difficult to address.[95,104]

Central poststroke pain is neuropathic in origin. Damage to the thalamus results in persistent pain in a high percentage of patients, but lesion size and location are not consistent predictors of pain; in fact, neuropathic pain is associated more commonly with partial injury to the spinothalamic tract than with complete lesions of the tract.[35,95,104]

In contrast, complex regional pain syndrome is divided into 2 subsets of pain types. This syndrome can arise as either neuropathic pain (given that it is recapitulated in most animal models through damage to a peripheral nerve) or as nociplastic pain that develops in the absence of direct injury to a nerve (which is the type most commonly seen in stroke patients).[104] However, this pain syndrome may, in fact, be neuropathic in origin more often than is recognized currently and may stem from muscle flaccidity and an inability to protect the shoulder joint after stroke. In this regard, strictly protecting the shoulder from subluxation and painful positioning reduced the incidence of this pain syndrome in human stroke patients from 27% to 8%.[104]

Another common sequela to CNS lesions involving upper motor neurons is muscle spasticity, which is defined as involuntary, often painful contraction of muscle groups from an exaggeration of the stretch reflex.[22] If not adequately addressed to maintain mobility, spasticity will progress to contractures of muscle bodies and tendons that are often quite painful.[22] This particular musculoskeletal pain syndrome is neuropathic in origin, but a case can be made for considering it nociceptive pain as well, given that the nociceptors in muscle and tendon are responding to the contracted state.

Protecting humans and animals from damage to their joints during anesthesia-induced laxity has been a known component of appropriate perisurgical care for many years, if not decades. This vulnerability may persist past the anesthetic recovery period in stroke or brain-injured patients, whether human or animal. Researchers must take care to recognize that their subjects may be unable to protect their joints. More recently, physical therapy has become a major component of rehabilitative care in companion animal veterinary medicine; in long-term brain injury studies, physical therapy can be expected to provide value in preventing or relieving musculoskeletal pain in laboratory animals as well.

Effects of Pain on the CNS and Peripheral Nervous System

An injury creates pain signals, either nociceptive or neuropathic in origin or both. In response to pain, the nervous system releases analgesic endogenous opioids.[89] As described previously,[77] the nervous system also releases the catecholamines epinephrine and norepinephrine (also known as adrenaline and noradrenaline, respectively). In the endocrine system,

glucocorticoids are released, elevating systemic levels of cortisol (or corticosterone, depending on species). Increased cortisol, epinephrine, and norepinephrine activate monocytes and drive additional changes in the immune system such as increases in IL10, decreases in IL12, and the conversion of TH1 to TH2 cells. In addition, elevated cortisol levels drive apoptosis of lymphocytes and eosinophils, decreased extravasation of inflammatory cells, and inhibition of neutrophil function, and decreased production of proinflammatory molecules. These changes have been well documented to slow the innate immune response to infection as well as healing.[77]

Whether acute or chronic, elevated levels of cortisol or corticosterone cause changes in neuronal activity and thus respectively depress or increase seizure activity—a fact well recognized in the field of epileptic medicine.[56] A thorough overview of how stress-induced plasticity affects GABA-driven inhibition has been published[58] and addresses restraint stress, social isolation stress, and other stressors. The mechanisms at play include alterations in the expression of subunits of $GABA_A$ receptors that are specific to particular brain regions (hippocampus, frontal cortex, and paraventricular nucleus in the hypothalamus); changes in chloride homeostasis due to downregulation of the potassium–chloride cotransporter KCC2; and synaptic plasticity at GABAergic synapses. All of these mechanisms alter the tonic inhibition of GABAergic pathways. At the receptor level, therefore, stress drives the somatosensory and visceral pain pathways toward hypersensitivity.[115] Both stress and anxiety are well-established human factors leading to sensitization of central pain pathways and heightened experience of pain,[118] and the considerable overlap between chronic pain and chronic stress has been reviewed at length.[1] Best practices for study of stroke and TBI include the control and minimization of pain and associated stressors—not only for humane reasons but also for clarity in the research itself.

Effects of Analgesics and Anesthetics on the Nervous System

It is beyond the scope of this review to comprehensively evaluate every drug that could potentially be used during the creation or maintenance of models of stroke or TBI and to present every potential therapeutic's effects on the CNS and neuroinflammation. However, excellent and thorough reviews are already available[33,89] and are summarized here. Overall, every analgesic and anesthetic in use should be expected to influence neuronal survival through changes to neuronal metabolism, either directly at the cellular level or indirectly at the circulatory level. Regardless of whether such mechanisms have been elucidated, veterinarians and researchers are well-advised to review the current literature prior to designing mechanistic or novel therapy studies of stroke or TBI, in order to develop a therapy reflective of the current best practices for human patients.

Effects of Previously Administered Analgesics and Anesthetics

It is widely recognized that prior exposure to opioids can induce opioid tolerance, requiring escalation of doses to achieve the desired effect. Opioid analgesics block the transmission of pain signals in the pain pathway at the level of the synapse, and an excellent review on opioid mechanisms[18] is available and summarized here. The main opioid receptor associated with analgesia, the μ-opioid receptor, is a G protein-coupled receptor located both pre- and postsynaptically at the first synapse in the spinal cord. Inhibitory G-protein-coupled receptors recognize a specific signaling molecule. Endogenous opioids are mimicked by morphine and other opioids, and these drugs differentially activate a 3-component G protein inside the neuron. The β and γ subunits of the G protein increase potassium channel conductance, decrease calcium channel conductance, and inhibit adenylyl cyclase. The overall effect of these actions is to decrease the release of excitatory transmitters and the excitability of the postsynaptic neuron, thereby muting the transmission of the pain signal. Unfortunately, chronic exposure to opioids leads to tolerance, where increased doses of opioids are required to achieve the same effect as initially observed in the patient. Various mechanisms have been proposed for development of tolerance: endocytosis, recycling, phosphorylation-driven desensitization, and association of the μ-opioid receptor with β-arrestin 2. Multiple mechanisms are thought to be involved.

Given that studies of brain injury often require the placement of implanted leads or other devices, it is important to consider the nuances of prior exposure to anesthetics as well. For example, in most studies, isoflurane preconditioning[116] shows improved outcomes,[42] as does extending the duration of exposure[24] to isoflurane. However, preconditioning an animal with isoflurane to a level of deep sedation prior to the induction of brain injury can lead to increased cortical damage and a worse neurologic outcome compared to animals which were preconditioned with isoflurane to a level of regular sedation.[32] However, the evidence is contradictory,[43] because although most work shows isoflurane has a neuroprotective effect,[89] other work showed no evidence of effect.[20] Because prior exposure to analgesics and anesthetics is built into the design of some research models, it is reasonable and useful to evaluate multiple-exposure regimens in light of their effects on neuronal survival after injury. This influence might perhaps be evaluated by including behavioral or postmortem analysis of a cohort of animals that received injury and therapy without any preinjury surgery.

Effects of Currently Administered Analgesics and Anesthetics

NSAID suppress inflammation by inhibiting COX1 and COX2, the enzymes that are responsible for converting arachidonic acid into inflammatory prostaglandins. However, chronic administration of NSAID has been shown to have inconsistent outcomes—sometimes protective but other times deleterious. In one study,[103] postoperative carprofen (5 mg/kg SC daily for 7 d) provided neuroprotective effects in a model of TBI in adult male Sabra mice. In a second study,[38] administration of the opioid buprenorphine (0.05 mg/kg SC at 1 h before and 8, 16, 32, and 48 h after surgery) demonstrated no effect on infarct size from ischemia due to middle cerebral artery occlusion in male C57BL/6 mice, whereas meloxicam (5 mg/kg SC at 1 h before and 24 h after surgery) reduced infarct size in the same study. In contrast, a third study[8] demonstrated that postoperative ibuprofen (25 or 50 mg/kg daily for 4 mo) expanded infarct size relative to no treatment in male Sprague–Dawley rats with TBI.

The evidence regarding whether inhalant anesthetics enhance[33] or decrease[89] cerebral blood flow after injury is conflicting. This apparent discrepancy may have less to do with the use of inhalant anesthesia and more to do with the type of injury sustained and whether it is hemorrhagic or ischemic in nature. As a sole agent, propofol decreases cerebral blood flow; yet when propofol is given in combination with an inhalant anesthetic, cerebral blood flow can be preserved.[33] Likewise, N_2O appears to enhance cerebral blood flow.[33] Another mechanism that influences blood flow after ischemic injury is known as reflex cerebral autoregulation; inhalant fluorinated anesthetics

(isoflurane and related drugs) are known to interfere with this reflex.[33] Propofol appears to have no effect on reflex autoregulation in a normal brain, but the reflex disappears in a traumatized brain under propofol anesthesia.[33] The benzodiazepine midazolam appears to preserve reflex autoregulation, whereas the α2-adrenergic agonist dexmedetomidine appears to abolish it.[33]

One therapeutic method that is used to minimize the zone of neuronal death is to decrease the cerebral metabolic rate (as often measured by glucose metabolism). Mild hypothermia slows the metabolic rate of neurons, as do inhalant anesthetics, propofol, benzodiazepines, lidocaine, dexmedetomidine, etomidate, and fentanyl (in low doses);[33,89] however, this effect can be dose-dependent, given that both alfentanyl and high doses of fentanyl increase the metabolic rate and may precipitate seizures.[33] As a class, barbiturates have primary action on the $GABA_A$ receptor[37] and are known to decrease the cerebral metabolic rate.[85] N_2O increases the metabolic rate when given as a single agent but appears to decrease the metabolic rate when given in combination with other inhalant anesthetics.[33] Ketamine predominantly acts as an NMDA receptor antagonist and can increase or decrease the cerebral metabolic rate, depending on the region of the brain.[74,107] In addition, ketamine appears to have subtype-specific actions on $GABA_A$ receptors, acting on extrasynaptic receptors without significant effect on synaptic receptors; this effect results in potentiation of tonic inhibition that may contribute to its neurodepressive effects.[108] Because inhalant anesthetics, barbiturates, and propofol have increased potency at $GABA_A$ receptors and because nitrous oxide and ketamine have few or selective effects, the cerebral metabolic rate might be related to certain $GABA_A$ receptor effects.[33]

Excitotoxicity seems to be lessened in animals given isoflurane, propofol, and perhaps ketamine.[33] Spreading depolarizations are reduced by inhalant anesthetics, N_2O, and ketamine when compared with propofol, opioids, and midazolam. The onset of spreading depolarizations can be delayed by using barbiturates, inhalants, and centrally administered lidocaine.

Opioids have various effects on intracranial pressure, cerebral perfusion pressure, and mean arterial pressure, thus in turn affecting neuronal survival, as already discussed. In one review,[111] the apparently inconsistent effects of morphine, fentanyl, and other opioids in cases of TBI were suggested to likely reflect (at least in part) the heterogeneity of the injury. Future studies are warranted to elucidate opioid effects on short- and long-term neuronal survival.

To arrive at a general consensus regarding the effects of different postoperative analgesic classes on distinct CNS injuries, additional comprehensive studies inclusive of a broad spectrum of species, strains within species, and both sexes is necessary.[38] To our knowledge, such a survey has yet to be reported. In the absence of such a survey, introducing overarching guidelines for postoperative pain medications might greatly limit advances in both mechanistic and efficacy research, even when such guidelines are carefully designed to mimic current clinical therapy and minimize effects on model development.

Summary

When presented with a patient experiencing stroke or TBI, clinicians seek to halt further damage, minimize lesion size and save neurons. To aid healthcare providers, the overarching goals of stroke and TBI research are 1) to define mechanisms of neuronal damage and loss and 2) to develop novel therapies to address them.

Modeling central neurologic injury induces a predictable spectrum of pain. It is easiest to anticipate development of nociceptive pain because this pain arises from the surgery or trauma itself as well as any subsequent muscle spasticity that might occur. The classic categories of analgesics (NSAID, opioids, and local anesthetics) are appropriate therapies to prevent or ameliorate nociceptive pain. In addition, investigators should anticipate the development of both neuropathic pain and nociplastic pain in their research subjects. Addressing these types of pain may require the use of adjunctive medications, such as α_2-adrenergic agonists, NMDA antagonists, anticonvulsants, and antidepressants. Furthermore, anticoagulants and nonmedication options such as physical therapy might comprise useful components of a care regimen. To select appropriate medications when designing the perioperative and postoperative care for a given injury model, researchers and laboratory animal veterinarians are well advised to review the research literature regarding each drug considered.

Many factors drive differences in postneurologic injury outcomes between individual animals. It is neither feasible nor ethical to attempt to incorporate sufficient nontreated groups in a given study to control for all possible variations. Instead, it is humane and respectful of resources to provide all animals with consistent medical care that, as much as possible, parallels the standard of care in human patients, allowing only the study article to differ. In addition to the vehicle groups so useful in the study of novel therapies, sham-injury groups should be included in both mechanistic research as well as novel-therapy research. These animals would receive the same care in the absence of neurologic injury and thus enable researchers to distinguish between effects of clinical therapy compared with effects of injury. When attempting to distinguish between the effect of the prescribed medications as compared with a novel therapeutic, another option is to use 2 distinctly different anesthesia and analgesia regimens to discern which part of the outcome can be attributed to the study article.

To enhance research reproducibility and evaluation, all planned and unplanned therapeutic measures should be published. Together with details regarding the injury model itself, information including dose, route, frequency, and response to therapy should be reported. Communication with human patients who have experienced stroke or TBI regarding their postinjury pain represents an important starting point for the design of preclinical models for exploring the nature of and mechanisms underlying postinjury pain. In addition, therapeutic approaches effective at reducing this pain in humans can inform preclinical modeling of therapeutic approaches. Going forward, this type of reverse translation likely will be a productive approach.

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