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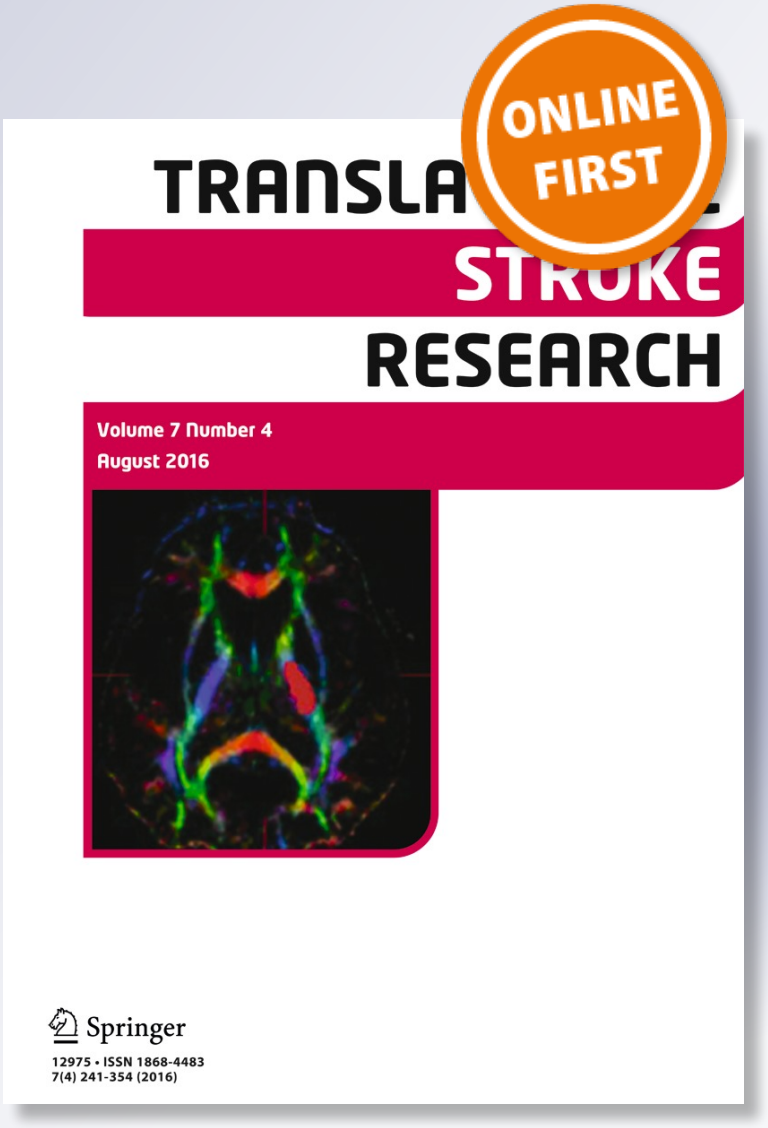

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ORIGINAL ARTICLE

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Abstract Anesthetics have enabled major advances in development of experimental models of human stroke. Yet, their profound pharmacologic effects on neural function can confound the interpretation of experimental stroke research. Anesthetics have species-, drug-, and dose-specific effects on cerebral blood flow and metabolism, neurovascular coupling, autoregulation, ischemic depolarizations, excitotoxicity, inflammation, neural networks, and numerous molecular pathways relevant for stroke outcome. Both preconditioning and postconditioning properties have been described. Anesthetics also modulate systemic arterial blood pressure, lung ventilation, and thermoregulation, all of which may interact with the ischemic insult as well as the therapeutic interventions. These confounds present a dilemma. Here, we provide an overview of the anesthetic mechanisms of action and molecular and physiologic effects on factors relevant to stroke outcomes that can guide the choice and optimization of the anesthetic regimen in experimental stroke.

Keywords Anesthesia · Anesthetic · Brain · Ischemia · Stroke

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Introduction

There is strong evidence that sufficient overlap exists between the neurobiology of disease in laboratory animals and humans to justify definition of therapeutic safety and efficacy parameters in preclinical models to inform rational clinical trial design [1]. Surgically created disease models allow study of injury mechanisms and identification of therapeutic targets. In vitro and invertebrate systems can provide critical information regarding molecular mechanisms of injury but cannot substitute for in vivo models. We still need to investigate these phenomena and confirm their relevance in intact mammalian systems where interactions between local, remote, and humoral factors contribute to the outcome of central nervous system (CNS) injury. Acute human CNS injury, such as ischemic or hemorrhagic stroke, trauma, and global hypoxic ischemic injury, largely occurs in the absence of anesthesia. Anesthesia and analgesia are necessary to assure animal welfare while reproducing brain injury in the laboratory, but the implications of anesthetic/analgesic use in experimental CNS injury are often ignored or misunderstood. The impact of anesthetic/analgesic use on model outcomes may substantially confound our understanding of the neurobiology of acute brain injury, posing a significant dilemma. Conversely, some treatments for acute human stroke may involve anesthesia (e.g., hemicraniectomy, carotid endarterectomy or stenting, cerebral aneurysm clipping/coiling, mechanical thrombolysis). The extent to which clinical anesthetic exposure alters the course of disease and how this should be modeled experimentally has long been investigated, providing a wealth of information of relevance to model nonoperative disease [2]. There also is strong evidence that neurobiological effects of anesthetics are not transient. Potent effects on preconditioning and postconditioning, excitotoxicity, apoptosis, neurogenesis, gene regulation, neurodevelopment, and short- and long-

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term outcome from ischemic insults have been widely reported. Here, we aim to provide a review of anesthetic modulation of CNS and systemic physiology relevant to experimental stroke to help define potential confounders of model outcomes used for clinical translation.

Resting Cerebral Blood Flow and Metabolism

Historically, as a result of interest in aviation physiology, methods were developed in the 1940s to measure cerebral blood flow (CBF) and metabolic rate (CMR) in humans [3], followed by exploration of anesthetic effects on these measures [4]. First, barbiturates were found to decrease CMR. Further work indicated that CMR reduction was maximal with onset of an isoelectric encephalogram (EEG) [5]. The mechanism of CMR reduction was attributed to inhibition of synaptic neurotransmission. Conservation of the energy required to support neurotransmission was postulated to increase tolerance to ischemia [6]. Extensive research has since been conducted across the spectrum of anesthetics for effects on CMR in both humans and laboratory animals. A consistent pattern is observed. Isoflurane [7], sevoflurane [8], propofol [9], benzodiazepines [10], etomidate [11], lidocaine [12], fentanyl [13], and dexmedetomidine [14] cause a dose-dependent generalized decrease in CMR. Maximal anesthetic-mediated CMR suppression ranges from 30 to 60 % of baseline.

In contrast, ketamine, a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, causes heterogeneous CMR changes. In humans, CMR is increased in the frontomedial and anterior cingulate cortex, but decreased in other regions [15]. Similar region-specific effects of ketamine have been reported in the rat [16]. Nitrous oxide (N_2O) can cause a major CMR increase when given alone, although this may be dose- and species-dependent [17, 18]. Like ketamine, the effect of N_2O on CMR is regionally heterogeneous [19]. When combined with other anesthetics, N_2O produces variable CMR effects [20, 21]. Lastly, high doses of alfentanil and fentanyl (typical of most opioids) can precipitate status epilepticus and markedly increase CMR [22].

Differential effects on CMR may be related to anesthetic mechanism of action. While most all anesthetics have a measurable effect on both $GABA_A$-ergic and glutamatergic systems, the spectrum of potency for individual anesthetics across neurotransmitter systems varies markedly. Volatile anesthetics, and most hypnotics (e.g., propofol, barbiturates), exhibit more potent effects at the $GABA_A$ receptor [23] with only weak inhibition of glutamatergic activity [24], and cause a dose-dependent decrease in CMR generalized across brain regions. In contrast, ketamine and N_2O are predominantly noncompetitive NMDA receptor channel blockers with negligible effects on $GABA_A$ receptors [25–28], and both induce regionally heterogeneous increases and decreases in CMR. Xenon differs, perhaps because it serves as a NMDA receptor antagonist by competitively inhibiting the glycine site [29]. While this likely contributes to improved stroke outcome [30], unlike the heterogeneous CMR effects of ketamine and N_2O, xenon causes a consistent decrease in CMR across a broad range of brain regions [31].

Besides indirectly influencing CBF via altered CMR, anesthetics can exert vasomotor effects through endothelial and smooth muscle mechanisms [32–34]. For example, in humans subjected to propofol-induced EEG isoelectricity, where anesthetic-mediated CMR suppression would be maximal [35], addition of equivalent doses of halothane, isoflurane, and desflurane all increased CBF, indicating direct pharmacologic effects on cerebral vascular tone. N_2O also increases CBF whether used alone or in combination with other anesthetics [17, 36]. Further, anesthetics may differentially alter CBF/CMR coupling. Volatile anesthetics decrease CMR but increase CBF, while most intravenous anesthetics decrease both. Although it is tempting to consider an uncoupling of flow and metabolism by volatile anesthetics, several studies have shown that coupling is preserved, although the ratio of flow to metabolism is altered in a dose-dependent fashion [37, 38]. Both direct and indirect vascular effects may be important considerations when selecting anesthetics in various experimental (or clinical) conditions.

Cerebral Blood Flow Autoregulation

Autoregulation maintains CBF within physiological limits across a wide range of cerebral perfusion pressures. Autoregulation also is a critical vasodilator reflex that helps augment collateral blood supply when the occlusion of a cerebral artery creates a low perfusion pressure state within and surrounding ischemic tissue. Volatile anesthetics impair autoregulation. Halothane abolished autoregulation at 1 MAC (minimum end-tidal alveolar concentration at which 50 % of subjects continue to respond to a noxious stimulus with a motor response) in the healthy goat [39], whereas 2 MAC was required for isoflurane and sevoflurane to abolish autoregulation in the dog and rat, respectively [40, 41]. Similar effects for sevoflurane, isoflurane, and desflurane have been observed in humans [42, 43]. N_2O also impairs autoregulation [44]. Intravenous anesthetics have less effect on autoregulation. Propofol does not impair autoregulation in normal baboon or human brain [9, 42]. However, propofol doses approaching those used for surgical anesthesia abolish residual autoregulation in traumatized human brain [45]. Racemic ketamine does not abolish porcine autoregulation [46], as is also true of the S(+)-ketamine enantiomer in rats [47] and humans [48]. Human dynamic autoregulation is improved by midazolam [49], but dampened by dexmedetomidine [50]. Little or

no exploration of the effects of these drugs on autoregulation has been made in ischemic brain.

Thus, use of inhaled anesthetics (N_2O, isoflurane, sevoflurane, and desflurane) can produce an abnormal cerebrovascular responsivity to perfusion pressure changes in normal brain, which is dose-dependent and likely relevant at surgical concentrations. Intravenous anesthetics are more likely to preserve autoregulatory responses. While effects of anesthetics on CBF have typically been measured under steady state conditions, dynamic changes in flow are likely to induce variability in severity of an ischemic insult if the surgical preparation is hemodynamically unstable and autoregulation is impaired. If this is of importance to the investigator, use of an intravenous anesthetic or low-dose volatile anesthetic would seem most likely to diminish perfusion artifacts. Should a volatile anesthetic be preferred, doses sufficient to provide surgical anesthesia could be decreased upon completion of surgery, after instillation of local anesthetic into the surgical wound, to maintain appropriate immobilization and minimize disruption of cerebrovascular responsivity to changes in perfusion pressure.

Ischemic Depolarizations

Ischemic (i.e., anoxic) depolarization is arguably the most important and often terminal step in the progression of acute ischemic injury, marking the depletion of ATP stores and loss of transmembrane ionic gradients. Numerous anesthetics have been tested to delay the time to depolarization, because their inhibitory effect on CMR is expected to slow ATP depletion in ischemic tissue. Using either in vivo or in vitro preparations, lidocaine [51], thiopental [52], pentobarbital [53], propofol [54], isoflurane [55], desflurane [56], and sevoflurane [57] have all been reported to delay depolarization onset.

Whether CMR reduction alone is sufficient to explain anesthetic-induced delay in ischemic depolarization is unclear. However, when rats were subjected to severe global ischemia, onset of depolarization occurred 1.5 min slower if isoflurane was used compared to halothane at equi-anesthetic doses [58]. This is consistent with the known greater CMR suppression provided by isoflurane. Such differences appear to translate to outcome as well. For example, rats subjected to 6 min of severe forebrain ischemia had less hippocampal CA1 damage with isoflurane compared to an equi-anesthetic halothane dose. Increasing ischemia duration to 7.5 min during isoflurane anesthesia produced the same magnitude of CA1 damage seen with 6 min ischemia during halothane anesthesia [59].

Additionally, in focal cerebral ischemia, recurrent spreading depolarizations (SD) occur in peri-infarct tissue and expand the infarct in a stepwise fashion over time [60]. SD frequency is anesthetic dependent. In experimental preparations, pentobarbital, urethane, and propofol do not substantively suppress SD frequency [61], whereas inhalational anesthetics (e.g., isoflurane, halothane, N_2O) and dexmedetomidine do [61–65]. In humans, ketamine, N_2O, and isoflurane suppress peri-infarct SD frequency compared with propofol, opioids, or midazolam [66, 67].

Ischemic Outcome

Historically, the translational pathway for anesthetic neuroprotection has gone from bedside to bench because anesthetics are clinically available. Early studies were driven by the question of which anesthetic might do the least harm, or even provide benefit if given to patients with acute or potential CNS injury. It has been difficult to predict the net effect of anesthetics on stroke outcome, given the heterogeneous effects on resting CMR and CBF, autoregulation, and peri-infarct SDs. Although one would expect the anesthetic-induced decrease in CMR to afford neuroprotection [68, 69], there is negligible clinical evidence to support this claim. Human trials to test this have been mostly negative, and those few that were positive could not be reproduced [70]. However, the majority of these clinical trials would not meet current standards of design and execution, and some have been simply comparative studies of one anesthetic versus another. Therefore, lack of clinical evidence should be interpreted cautiously, as laboratory data suggest otherwise.

Volatile Anesthetics

Isoflurane has been shown to be protective against excitotoxicity. For example, primary mixed neuronal/glial cell cultures exposed to NMDA exhibited less LDH release in the presence of volatile anesthetics [71]. This was consistent with in vivo data indicating that isoflurane ameliorates excitotoxicity induced by microinjection of either NMDA or AMPA into the cortex of rats [72, 73]. In cortical brain slices subjected to anoxia, glutamate release was decreased by isoflurane, the magnitude of which was similar to hypothermia (28 °C) [74]. When organotypic hippocampal slices were exposed to oxygen-glucose deprivation, delayed neuronal necrosis was inhibited by isoflurane, which was as effective as moderate hypothermia (34 °C) [75]. Isoflurane neuroprotection was later attributed to a $GABA_A$-ergic mechanism and regulation of intracellular calcium [76, 77].

For in vivo studies, volatile anesthetic efficacy is model dependent. Rats anesthetized with isoflurane demonstrated major histologic protection (by more than 50 %) and improved 8-week functional outcome in a filament MCAO model compared to rats that were unanesthetized for the majority of the duration of ischemia, while controlling for the pericranial temperature and arterial perfusion pressure during MCAO and reperfusion [78]. Sevoflurane also improves focal ischemia outcome [79]. In

hemispheric ischemia, rats had improved long-term functional outcome when anesthetized with sevoflurane when compared to fentanyl/N_2O [80]. In a severe forebrain ischemia model, isoflurane was found to only transiently improve functional and histologic outcome [81]. This is consistent with other work in focal ischemia that identified inhibition of necrosis by isoflurane, but failure to inhibit apoptotic injury most likely generated from ongoing ischemia [82]. It is upon anesthetic backgrounds similar to these that stroke therapeutics are often evaluated for preclinical efficacy. The interaction between anesthetic neuroprotection and the purported stroke therapeutic is typically not considered. Although volatile anesthetics will likely continue to be favored in experimental stroke research for their ease of use and rapid reversibility, these results suggest that their use is likely to introduce major confounds in study of experimental stroke mechanisms and outcome.

Nitrous Oxide

N_2O is an NMDA receptor antagonist [83] and has received some attention as a neuroprotective agent. However, in a filament MCAO model, intra-ischemic N_2O did not alter histologic or neurologic outcome when compared directly to the same fractional inspiratory concentration of nitrogen (70 %) [84]. When given after MCAO reperfusion, N_2O has been reported to improve outcome, but a narrow therapeutic window of less than 3 h was evident and long-term outcome was not studied [85, 86]. In contrast, 70 % N_2O worsened outcome when administered during an intermediate duration of global forebrain ischemia in gerbils (5 min), while no effect was observed in either brief (3 min) or prolonged (7 min) ischemic insults [87]. In a large human trial involving temporary vessel occlusion during cerebral aneurysm clipping, N_2O increased the frequency of delayed ischemic deficits, but an effect on long-term neurologic or neuropsychiatric outcome was not detected [88]. Altogether, these data do not support a substantive neuroprotective effect of N_2O in cerebral ischemia.

Intravenous Anesthetics

Barbiturates have been reported to ameliorate focal ischemic injury [89]; however, the overall benefit appears to be modest in thermoregulated animals [90]. Effects in global ischemia are inconsistent and likely model dependent [91, 92]. The efficacy is often attributed solely to CMR reduction, although this has been disputed [90]. Barbiturates constitute a family of compounds, for which free radical scavenging [93], anticonvulsant properties [94], and attenuation of glutamate accumulation [53] have been reported. Ketamine has been widely studied as a noncompetitive NMDA receptor antagonist with potential to limit excitotoxicity [95], but effects on ischemic outcome have been inconsistent [96–99], in part due to lack of brain temperature control [100, 101]. Nevertheless, ketamine is protective against ischemia in vitro as well [102], suggesting potential temperature-independent effects. Propofol not only decreases CMR and CBF but also offers other properties including mitigation of excitotoxic and oxidative stress [103, 104], apoptosis [105], inflammation [106], and autophagy [107]. Results of preclinical efficacy studies have been mixed. Propofol has been reported to be beneficial in focal [108, 109], hemispheric [110], and global [111–113] ischemic insults. These positive results have been countered by other work, which failed to detect an effect on outcome in vivo [114–116] or in vitro [52]. α-2-Agonists are a class of compounds including dexmedetomidine, clonidine, and xylazine. α-2-Agonists are commonly employed in veterinary anesthesia across a broad range of species. Although analgesic properties are present, there is a ceiling effect. Hence, surgical anesthesia typically requires use of a supplemental analgesic such as ketamine or an opioid. The most extensive investigation for α-2-agonist effects in experimental stroke has been on dexmedetomidine, possibly because it is also commonly used for human anesthesia. Dexmedetomidine has generally been reported to improve ischemic outcome across a range of species [117, 118], although adverse effects of dexmedetomidine-induced hypotension on intra-ischemic CBF have been noted [119].

As with any pharmacological intervention, conflicting results are likely due to the presence of multiple mechanisms of action often counteracting each other, and ischemic outcomes also depend on the experimental model and study design. Lack of a systematic dose-response analysis further complicates interpretation.

Other Anesthetics and Analgesics

Desflurane, etomidate, urethane, alpha-chloralose, chloral hydrate, and opioids and their combinations have also been investigated for neuroprotective properties or interactions with molecular and cellular responses to ischemia [2, 120, 121]. As a generalization, desflurane appears protective, μ-opioid agonists have little effect, and etomidate may be adverse. Urethane, alpha-chloralose, and chloral hydrate remain insufficiently investigated. Postoperative analgesics and sedatives can also potentially confound preclinical research. For example, common analgesics (e.g., lidocaine [122], bupivacaine [123], nonsteroidal anti-inflammatory drugs [124, 125], and buprenorphine [126]) can modulate neural activity, inflammation, CBF, and apoptosis. Despite this, postischemic use of the partial μ-opioid agonist buprenorphine has been reported to have no effect on MCAO outcome in mice or rats [127, 128].

Anesthetic Preconditioning

Models of experimental brain injury may require anesthetic exposure for instrumentation prior to administration of the

primary insult. Research has consistently shown that anesthetic exposure (with or without surgical procedures) induces a complex response that can be highly protective against a subsequent primary CNS insult. Rats subjected to 1 h of halothane anesthesia, followed by 2 h MCAO, had markedly smaller infarcts than those receiving propofol for the same duration [129]. In contrast, there was no benefit from an 8-h pre-ischemic exposure to either halothane or propofol. That a brief anesthetic exposure improves the outcome of a cerebral ischemic insult has been extended to isoflurane [130],

Table 1 Practical considerations for the choice of anesthetic regimen in experimental stroke

Anesthetic	rCMR	rCBF	AR	NVC	Other CNS effects	Cardiovascular	Respiratory	Other considerations
Volatile anesthetics	↓	↑	↓	↓	↑ $GABA_A$ receptor activation Improved Ca^{2+} homeostasis ↓ Spreading depolarizations	↓	↓[b]	Easy titration Rapid anesthesia onset and recovery Requires exhaust system
Nitrous oxide	↑↓[a]	↑	↓	↓	↓ NMDA receptor activation ↓ Spreading depolarizations	Myocardial ↓ Sympathetic tone ↑	Negligible ↓	Additional hypnotic/analgesic required Accumulates in closed gas spaces
Propofol	↓	↓	↔	↔	↑ $GABA_A$ receptor activation Antioxidant ↔ Spreading depolarizations	↓	↓[c]	i.v. only Continuous infusion required Prolonged anesthesia emergence
Ketamine	↑↓[a]	↑↓[a]	↔	↓	↓ NMDA receptor activation ↓ Spreading depolarizations	Myocardial ↓ Sympathetic tone ↑	Minimal ↓[b]	Repeated dosing required Adjunct anesthetics required (opioid, benzodiazepine)
Urethane	↑↓[a]	↓	↔	↔	↑ Spreading depolarizations	↓	↓[b]	i.p./i.v./p.o. Unpredictable and long duration Hyperglycemia Mutagenic and carcinogenic Metabolic acidosis at high doses Suitable for nonsurvival experiments
α-Chloralose	↓	↓	↔	↔/↓	↔ Spreading depolarizations	↓	↓	i.p./i.v./p.o. i.p. injection might cause ileus Adjunct surgical analgesic required
Barbiturates	↓	↓	↔	↔	↑ $GABA_A$ receptor activation ↔ Spreading depolarizations Antioxidant	↓	↓[b]	i.p./i.v. Painful injection, irritation at injection site Repetitive injections accumulate unpredictable anesthesia duration
Dexmedetomidine	Modest ↓	↓	↓	↔	α-2 agonist ↓ Spreading depolarizations	↓	Minimal ↓[b]	i.p./i.v. May require continuous infusion Additional surgical analgesic required Transient hypertension on induction
Opioids (fentanyl)	Modest ↓	Modest ↓	↔	↔	↔ Spreading depolarizations	Negligible ↓	↓[c]	Additional surgical hypnotic required Rodents require high doses

rCMR resting cerebral metabolic rate, *rCBF* resting cerebral blood flow, *AR* CBF autoregulation, *NVC* neurovascular coupling, *CNS* central nervous system

[a] Regionally heterogeneous

[b] Spontaneous ventilation possible

[c] Mechanical ventilation necessary for surgical depth of anesthesia

sevoflurane [131], dexmedetomidine [132] and chloral hydrate [133], including long-term (2–4 weeks) outcome [134, 135]. In contrast, alpha-chloralose may be devoid of this property [64], and ketamine may block ischemic preconditioning mediated by activation of the NMDA receptor [136]. Anesthetic preconditioning is effective if employed when given immediately prior to, or as early as 24 h before an ischemic insult [131]. Similarly, exposure to various anesthetics after the ischemic insult may confer sustained protection (anesthetic postconditioning) [137, 138]. Mechanisms of anesthetic preconditioning and postconditioning are numerous and remain under investigation. The extent to which this impacts studies designed to advance our understanding of the neurobiology of stroke or efficacy of purported interventions must be considered, particularly in the context of preclinical drug development.

Systemic Physiology and Other Factors

Most anesthetics depress myocardial contractility, systemic vascular resistance, and hence arterial blood pressure, which can be detrimental to ischemic tissue perfusion both at rest and during peri-infarct SDs [139–141]. Moreover, anesthetics are often respiratory depressants and promote airway obstruction, which may superimpose hypoxemia and hypercapnia on the ischemic insult. Finally, most anesthetics perturb thermoregulation and blood glucose concentration. Seemingly, trivial changes in any of these variables can have major impact on ischemic outcome. Therefore, systemic physiological monitoring is critical to avoid the confounding effects of anesthesia on ischemic outcomes and to reduce variation within and across laboratories.

Conclusions

Anesthesia is necessary to ensure animal welfare in experimental stroke models. Yet, it has profound and variable effects on neurobiology and systemic physiology. Anesthesia can be neuroprotective in part through modulation of ion channels and neural activity, metabolism, inflammation, apoptosis and autophagy, and peri-infarct SDs. Conversely, anesthesia can worsen ischemic outcome indirectly by causing, for example, hypotension or impaired autoregulation. As such, anesthesia has been among the confounders haunting translational stroke research. For example, if an anesthetic has already decreased cerebral infarct volume by direct neuroprotection, the efficacy of another drug tested in such a model can be masked. Or using an anesthetic that inhibits peri-infarct SDs can mask the effect of a potential therapeutic intended to suppress SDs. It is unrealistic to formulate a set of rules in recommending a fixed anesthetic regimen in all experimental stroke research. Instead, reproducing a therapeutic effect of a novel intervention under different anesthetic regimens would help reduce the confound. Investigators must be aware of potential CNS and systemic anesthetic effects and tailor the anesthetic choice, combination, and dosing based on the hypotheses being tested (Table 1). Finally, when reporting results from a stroke preparation, clear definition of the anesthetic management employed will allow others to consider anesthetic confounds inherent in the experiment. Continued efforts to understand mechanisms of anesthetic action in normal and diseased brain will serve to improve our use of experimental stroke models to advance patient care.

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Conflict of Interest None.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

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