Hypertonic Saline for Craniotomy?

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In this issue of Anesthesiology, Rozet et al.1 present the findings of a comprehensive study comparing two hyperosmolar agents, hypertonic saline (HS) and mannitol, for brain relaxation during craniotomy. This work calls into question whether sufficient information is now available to advocate substitution of mannitol with HS to promote brain relaxation during routine craniotomy. This work calls back of this issue. It was discovered in the early 20th century that HS reduces brain bulk in animals.2 Reports in humans were available to advocate substitution of mannitol with HS to promote brain relaxation during craniotomy. This work calls into question whether sufficient information is now available to advocate substitution of mannitol with HS to promote brain relaxation during routine craniotomy.

It was discovered in the early 20th century that HS reduces brain bulk in animals. Reports in humans were not forthcoming until the 1980s.3 The neurosurgical and neuro–critical care communities have since explored the use of HS because of its ability to treat cerebral edema and intracranial hypertension. Although mannitol remains the recommended hyperosmolar therapy in settings such as severe traumatic brain injury,4 HS is an appealing alternative because its reflection coefficient is superior to that of mannitol (1.0 vs. 0.9; i.e., HS does not cross an intact blood–brain barrier).5,6 HS also differs from mannitol in that it has little diuretic effect and thus should better maintain cerebral perfusion pressure.6 At the same time, HS and mannitol have similarities. Both agents have potential to improve blood rheology.4–7 This can serve to either reduce brain blood volume or improve flow through stenotic vessels. In contrast, in the presence of blood–brain barrier breakdown, both agents can accumulate over time in brain parenchyma and negate any beneficial effect or even increase intracranial pressure (ICP).5 The question, therefore, is whether HS offers efficacy superior to mannitol without adding risk.

Numerous studies have investigated the efficacy of different HS formulations (2–30% wt/vol) in the setting of neurologic injury.6 In contrast to the intraoperative investigation by Rozet et al.,1 the following studies compared mannitol with HS in neuro–critical care populations. Viale et al.8 performed a randomized comparative study of 20% mannitol and 7.5% NaCl, administered in equal volumes (not equiosmolar loads; 20% mannitol is approximately equivalent to 3% NaCl), to control ICP in 20 patients with traumatic brain injury. ICP control was better in the HS group, which received the higher osmolar load. Harutjunyan et al.9 randomly assigned 40 patients at risk for intracranial hypertension to receive 7.2% NaCl–hydroxyethyl starch 200/0.5 or 15% mannitol. Both drugs were continuously infused as required to maintain ICP less than 15 mmHg. 7.2% NaCl–hydroxyethyl starch 200/0.5 was more effective and had a greater osmolar load than 15% mannitol. A similar elevation in cerebral perfusion pressure was seen with both drugs (approximately 10 mmHg). Schwarz et al.10 compared equiosmolar loads of 20% mannitol versus 7.5% NaCl–6.0% hydroxyethyl starch for control of intracranial hypertension in nine ischemic stroke patients with 30 episodes of elevated ICP. Patients were randomly assigned to one or the other therapy and subsequent doses were alternated, mannitol or HS. The authors found HS to be more efficacious in controlling ICP, but the small sample size and potential crossover effects create limitations in interpreting the data. In a subsequent study, they found that 10% NaCl was effective in controlling ICP refractory to mannitol therapy in ischemic stroke patients.11 The use of HS as a rescue therapy for ICP refractory to mannitol has been reported by others.12 These studies, while providing insight, did not adequately assess the comparative efficacy of HS versus mannitol, due to either nonequiosmolar dosing or trial design.

In the operative arena, three previous investigations have been reported. These studies either did not use equiosmolar loads of mannitol and HS, or used a non–neurosurgical population.13–15 De Vivo et al.13 studied 30 neurosurgical patients randomly assigned to three groups: 3% HS, HS–mannitol, or 18% mannitol alone. Therapy was started intraoperatively and continued through postoperative day 3. ICP was decreased by all three strategies. Although 3% HS and 20% mannitol have similar osmolarity, the volumes of the respective solutions infused differed (and thus so did the osmolar load). Changes in serum sodium and potassium were inconsequential, but HS alone preserved central venous pressure better, consistent with the larger volume of HS given. Gemma et al.14 studied 7.5% NaCl versus 20% mannitol in equal volumes of 2.5 ml/kg (but different osmolar loads) in 50 elective craniotomy patients. They found that both therapies had similar effects on mean arterial pressure, central venous pressure, ICP, and brain bulk.
and concluded that the therapies were equally efficacious. Erard et al.\textsuperscript{15} conducted a pharmacodynamic study comparing equiosmolar mannitol and HS in 30 nonhemorrhagic surgical patients. Patients were randomized to hypertonic 20% mannitol, 7.5% NaCl, or isotonic 0.9% NaCl. They found that the osmotic changes over time were the same for both mannitol and HS and greater than for 0.9% NaCl.

The study by Rozet et al.\textsuperscript{1} in this issue of Anesthesiology is the first human study, to our knowledge, to compare equiosmolar loads of mannitol (20% wt/vol; 1,098 mOsm/l) and HS (3% wt/vol; 1,024 mOsm/l) for craniotomy. This prospective randomized blinded study compared the effects of 5 ml/kg 20% mannitol (n = 20), and 5 ml/kg 3% HS (n = 20), on brain relaxation during craniotomy. Half of the patients in both groups had aneurysmal subarachnoid hemorrhage, and the rest had craniotomies for elective surgery. Secondary endpoints included brain oxygen metabolism and electrolyte changes. Both treatments had similar effects on brain relaxation scores. There was no difference between groups in cerebral arteriovenous oxygen or lactate differences, arterial pH, central venous pressure, blood glucose, or plasma and cerebrospinal fluid osmolality. Mannitol had a greater diuretic effect, but arterial blood pressure values remained similar between groups. The mannitol group experienced a decreased fluid balance and increased arterial lactate concentration compared with HS. The HS group experienced increased plasma and cerebrospinal fluid sodium concentrations. ICP was not measured in this study. Therefore, this study provides a valid comparison of the efficacy of mannitol and HS in providing brain relaxation during routine craniotomy.

A number of patient safety concerns arise with the increasing adoption of HS in the perioperative arena. One is the issue of safely administering hyperosmolar solutions (HS or mannitol) through a peripheral intravenous catheter. Most elective craniotomy patients do not have central venous lines (which were placed in all patients, Rozet et al.).\textsuperscript{1} At our institution, pharmacy guidelines limit peripheral HS administration (maximum 2% NaCl; less than 1,000 mOsm/l) because of concerns for phlebitis and extravasation, although mannitol is allowed. There is little evidence on which to base this practice, and to the extent of our knowledge, there are no adequate data to assess the safety of peripherally administered mannitol relative to HS.\textsuperscript{16} There are case reports of forearm compartment syndrome from extravasated mannitol, although central venous catheters are certainly implicated in some extravasation injuries as well.\textsuperscript{17,18} HS (23.4% NaCl) is a venous sclerosing agent used in dermatology to treat superficial varicosities, and is known to cause skin necrosis with extravasation.\textsuperscript{19}

Second, is a patient with baseline hyponatremia at risk for central pontine or extrapontine demyelination from the use of HS? Hyponatremic patients were specifically excluded from the study of Rozet et al.\textsuperscript{1} and most other HS trials. Although central pontine demyelination is attributed to rapid correction of hyponatremia with HS,\textsuperscript{20} central pontine demyelination has not been reported in clinical trials testing HS for other indications (i.e., fluid resuscitation, ICP control, or brain relaxation).\textsuperscript{6} A pediatric trial examined the brain postmortem and found no evidence for central pontine demyelination.\textsuperscript{21}

Next, HS therapy results in an elevation of plasma sodium and often a hyperchloremic metabolic acidosis with ongoing therapy (unless formulated with acetate).\textsuperscript{6} Finally, plasma osmolality is frequently pushed beyond the traditional 320-mOsm/l limit during the use of HS (as well as with mannitol, for that matter). Despite these concerns and others, there is little evidence for harm with HS from the existing literature (other than in the chronically hyponatremic patient).\textsuperscript{22} Interestingly, Rozet et al.\textsuperscript{1} used a second 5-ml/kg bolus if needed to provide adequate brain relaxation (6 patients in each group received this). A patient could receive up to 10 ml/kg 3% HS or 20% mannitol (2 g/kg). Unless the clinical scenario is dire, this aggressive approach cannot be recommended without monitoring plasma osmolality. However, this practice does speak to the apparent safety of these agents and common practice by neuroanesthesiologists and neurointensivists to push beyond the conventional non–evidence-based safety limits. At the same time, Rozet et al.\textsuperscript{1} exposed only 20 patients to 3% HS, and therefore, the sample size was insufficient to allow comparison of adverse events, which are infrequent.

The authors have made a novel and major contribution to this field by comparing equiosmolar doses of mannitol and HS for brain relaxation during craniotomy. One can conclude from this study that it is the osmotic effect of the agent that results in brain relaxation and that both agents are equivalent in this regard. This is supported by the previous literature cited above where the hypertonic agent given in greater osmolar dose had greater efficacy in decreasing ICP.

Future larger-scale trials will be needed to address the impact of HS versus mannitol on clinical outcomes, probably by comparing longer-term use of the two agents for ICP control in traumatic brain injury and various types of stroke (subarachnoid hemorrhage, ischemic stroke, and intracerebral hemorrhage). Quantitative endpoints (i.e., ICP rather than brain relaxation) will need to be included in these studies, and the issue of bolus administration versus continuous infusion will need further investigation. The time is ripe for the neuroanesthesia and neuro–critical care communities to start registries of therapies such as HS that will allow for the detection and quantification of uncommon adverse events.

In conclusion, neuroanesthesiologists and neurointensivists should add HS to their pharmacologic armamentarium but should do so with caution with regard to

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Experience ≠ Expertise

Can Simulation Be Used to Tell the Difference?

An article in this issue of Anesthesiology raises a thorny issue for our specialty, and for organized medicine as a whole: the evaluation and maintenance of clinical competence of experienced clinicians. Murray et al.¹ report that board-certified anesthesiologists (BCAs) and anesthesiology residents performed similarly during a simulation-based assessment of acute intraoperative clinical skills. In a well-controlled experiment, 35 practicing anesthesiologists, of whom 91% were board certified, and 33 experienced anesthesia residents managed a series of critical events presented within brief (5-min) clinical scenarios in a high-fidelity simulated operating room. A separate group of 31 first-month CA1 residents each managed similar simulated events. Raters blinded to group viewed the videotaped performance in random order and ascertained whether the subject successfully performed predefined key diagnostic or therapeutic actions. As expected, the first-month residents’ performance was poorer than that of the more experienced groups. However, there were no significant differences in the overall performance between the experienced residents and the BCAs (26 from community and 9 from academic practices). All groups managed some critical events well (e.g., bronchospasm, tension pneumothorax) but had appreciable difficulty with others (e.g., malignant hyperthermia, hyperkalemia). There was large

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variability in the performance of individuals at all experience levels. Moreover, an individual's skill in managing one event did not necessarily predict his or her performance on other types of events.

Before interpreting these findings, we must review the study's limitations. The BCAs were self-selected from a single community and thus may not be representative of all experienced anesthesiologists. The BCAs were less familiar with the simulation environment than were the residents. However, before study initiation, they practiced doing a simulated induction and were provided time and resources to "set up" the anesthesia equipment and other resources within their simulated operating room as they wished. There did not seem to be any training (or order) effects on the BCAs' performance. In contrast, residents may have had more recent training in the management of similar critical events. Further, the scenarios were only 5 min in duration and thus may have lacked some key contextual factors associated with the ongoing care of actual patients. Yet, in an analogous situation, BCAs supervising certified registered nurse anesthetists or residents may be called urgently to an operating room to manage an evolving event. Each experienced clinician performed a different random combination of available scenarios, which varied in their clinical incidence and in their degree of difficulty. However, performance did not seem to be related to the frequency with which clinicians might deal with such events in actual practice. On balance, the scenarios and associated scoring criteria seem to have evaluated the kinds of acute management skills one might expect of experienced anesthesiologists.

Despite this study's limitations, I believe its findings are fundamentally valid and consistent with other research on the relation between clinical experience and quality of care. Experienced anesthesiologists, as a group, may not be nearly as expert at managing intraoperative critical events as some may have thought or would like. And, perhaps more importantly, there is tremendous variability in performance, not only between experienced practitioners, but also in the management of different types of events by the same practitioner.

Is Realistic Patient Simulation a Valid and Reliable Method of Assessing Clinical Competence?

In any performance evaluation, one must establish the validity of the scoring criteria (i.e., measuring the correct things) and the reliability of the scoring (measuring those things correctly). Some will legitimately argue that the simulated care environment is artificial and that performance during simulations may not reflect performance during actual clinical practice. However, few of our current alternatives (e.g., number of continuing medical education credits, hospital quality assurance reports, malpractice claims history) reliably measure the clinical competence of practicing physicians. Simulation-based assessment is still in its infancy. Before we use simulation for high-stakes assessments (e.g., board certification), substantially more research and development will be required to refine and standardize scenario content, scoring methods, evaluator training, and assessment protocols (e.g., number of scenarios per assessment). A randomized controlled trial of simulation-based assessment versus actual patient outcomes would be highly desirable but may not be feasible.

Experience Is Not Synonymous with Expertise

The evidence across many disciplines, from sports to medicine, suggests that experience is not synonymous with expertise. One might speculate that the BCAs in the study of Murray et al. either never attained the evaluated competencies or may have lost these skills during their years of clinical practice. Ericsson argues that most professionals attain only a mediocre level of performance during initial training and that performance level is, at best, only maintained during the rest of their careers. By definition, an expert consistently provides superior domain-specific performance. Expertise is more than simply having extensive factual knowledge or competent skills. Experts have specific psychological attributes such as self-confidence, excellent communication skills, adaptability, and risk tolerance. They also have specific skills, including highly developed attention to what is relevant, ability to identify exceptions to the rules, flexibility to changing situations, effective performance under stress, and ability to make decisions and initiate actions quickly based on incomplete data.

For clinical procedures, one can demonstrate a correlation between experience (number of procedures performed) and performance (number of errors). This relation is less clear for complex cognitive skills. Previous simulation studies provided only weak evidence that clinicians with more (or more recent) training manage untoward events more effectively.

Expertise can be very context sensitive. Expert management of one specific type of event (e.g., myocardial ischemia) will not necessarily generalize to other types of events (e.g., anaphylaxis)—even if many of the same cognitive and psychomotor skills are applicable. Moreover, clinical expertise is dynamic—it varies with the situations and the individual’s cognitive and emotional resources. A well-trained clinician, subjected to an event in a novel environment (e.g., new operating room or anesthesia workstation), may not perform at the same level as he or she would in a more familiar setting.
Training for, and Maintenance of, Expertise

Expertise seems to be most reliably formed and maintained through (1) motivation to improve, (2) focus on clearly defined tasks, (3) immediate useful feedback, and (4) repetitive deliberate practice strategically guided by an expert instructor.\(^5\) Notably, in other domains (e.g., sports, gaming), expertise primarily derives from countless hours of solitary and systematic practice typically characterized by careful study of one’s own and other experts’ performance, mindful emphasis on subtask performance, and increased challenges. Evidence suggests that, at least for the acquisition of procedural expertise, simulation may be an ideal approach.\(^1\)

From healthcare quality improvement, we know that outcomes are determined by process. Is physician training currently designed to generate clinical expertise? In fact, the current system does not support lifelong learning and improvement. Repeating the same actions and behaviors on a daily basis during routine clinical care, without deliberate practice, will not improve clinical performance.

Although still speculative, what may generalize across the management of different acute clinical events is training in "nontechnical skills": behavioral attributes of teamwork, communication, and resource management embodied in the simulation-based Anesthesia Crisis Resource Management curricula originated by Gaba \(^{et\, al.}\)\(^{12}\) Nontecnical skills can be reliably assessed.\(^{13}\)

What’s Next for Simulation-based Assessment?

Anesthesiology has been on the forefront of the use of high-fidelity simulation for clinical training, and increasingly, this strategy is supported by evidence.\(^{14}\) The recent meta-analysis by McGaghie et al.\(^{14}\) showed a strong positive correlation between hours of simulator practice and standardized learning outcomes. In the more controversial area of simulation-based assessment, other clinical specialties, especially nursing and family practice, are taking the initiative. American anesthesiologists could particularly learn from the experience of our Israeli colleagues, who have implemented mandatory simulation-based assessment in their national board certification examination.\(^{15}\)

Before one confidently undertakes simulation-based high-stakes assessment, it is essential to establish and agree on its content (what should be evaluated) as well as the examination’s scoring validity, reliability, generalizability, and “passing” criteria. Because of the complexity and dynamism of high-fidelity simulation, creating evaluation systems with acceptable psychometric properties is more difficult than for static evaluations (e.g., written examinations). How do you score a scenario where the correct things are done in the wrong order? If everything is done correctly except for one critical item? If performance varies substantially over time? Also, the dynamic interactions between trainee and simulation affect reproducibility; it may be impossible to predict and script a consistent response to every possible trainee action. Murray \(^{et\, al.}\)\(^{1}\) finesse some of these issues by using a small number of brief circumscribed scenarios and limiting participant–simulation interactivity. Such decisions enhance feasibility and reliability but at the potential expense of generalizability and validity.

An American Society of Anesthesiologists (ASA) Task Force, under the direction of Michael Olympio, M.D. (Chair, Workgroup on Simulation Education) struggled with these and other issues (e.g., performance anxiety, expense) as it created a program to provide standardized simulation-based courses to ASA members.\(^{8}\) In 2006, the ASA created a formal Committee on Simulation Education, chaired by Randolph H. Steadman, M.D. This Committee recently issued a call for applications for simulation centers to become “ASA Approved.” The American Board of Anesthesiology has been working closely with the ASA to foster the creation of simulation-based training experiences for Maintenance of Certification in Anesthesiology.

It is probably inevitable that anesthesiologists, as well as other medical professionals, will be required to participate in simulation-based training and competency assessment (including credentialing). There will be external pressures to do so—from the public, Joint Commission on Accreditation of Healthcare Organizations, government regulators, and even other specialties.\(^{10}\) The road ahead may be long and will be rocky. Thanks to two decades of leadership in medical simulation, our specialty is in a unique position to affect both the pace and direction of this journey. Murray \(^{et\, al.}\) are to be congratulated for taking an important step in the right direction. The next steps must include (1) a substantial investment in extramurally funded simulation research to establish valid content, structure, and scoring metrics; (2) collaboration with educators, psychometricians, and other specialties; (3) training of a larger cadre of skilled instructors/evaluators; and (4) a commitment to large-scale standardized training and assessment of medical students, residents, and experienced anesthesiologists.

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Noble Meets Nouveau

A Shared Anesthetic Binding Site for Xenon and Isoflurane on a Glutamate Receptor

XENON is of noble extraction, as old as the hills, ubiquitous but rare and elusive; it is present as a trace gas in earth’s atmosphere at only 0.05 ppm. Isoflurane, on the other hand, is a compound born in the atomic age, a polyhalogenated methyl ethyl ether crafted by Ross C. Terrell, Ph.D., in 1965 after advances in organic fluorine chemistry facilitated by development of the atomic bomb. Despite extreme differences in their structures and properties, both xenon and isoflurane have the striking ability to induce general anesthesia, although the mechanisms involved are far from clear. It is therefore remarkable that this noble gas and upstart organic chemical have now been found by Dickinson et al.2 to frequent the same binding site on the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor.

N-Methyl-D-aspartate receptors are major postsynaptic membrane receptors for glutamate, the principal excitatory neurotransmitter in the mammalian central nervous system.3 NMDA receptors, defined pharmacologically by their selective activation by the agonist NMDA, are a subtype of glutamate-gated ion channels that open to permit cation entry upon binding of the agonist glutamate (or NMDA) to an NR2 subunit and of the coagonist glycine to the NR1 subunit. NMDA receptors are involved in memory, pain, neurodegeneration, and cerebral ischemia as a result of their capacity to allow Ca2+ entry upon activation, hence their critical relevance to anesthesiology. This landmark study greatly advances our understanding of the mechanisms of general anesthetic interactions with NMDA receptors by identifying a novel binding cavity in the NR1 subunit for these two markedly different anesthetics.

Accumulating evidence indicates that there is no universal target that explains all actions of every general anesthetic, or even of a single anesthetic agent.4 Neurotransmitter-gated ion channels, particularly receptors for γ-aminobutyric acid (GABA) and glutamate, are modulated by most anesthetics, at both synaptic and extrasynaptic sites, while additional receptors and ion channels, such as specific Na+ and K+ channels, are also recognized as important targets. General anesthetics act as positive or negative allosteric modulators of these ion channels at clinically effective concentrations. Most inhaled anesthetics, including all of the volatile ether anesthetics (e.g., isoflurane, sevoflurane, desflurane, enfurane), some of the alkanes (e.g., halothane), and most intravenous anesthetics (e.g., propofol, thiopental, etomidate) enhance GABA[A] receptor function by increasing channel opening to enhance inhibition at both synaptic...
and extrasynaptic receptors. In addition to their prominent effects on GABA<sub>A</sub> receptors, volatile anesthetics selectively depress excitatory synaptic transmission presynaptically, where their principal action seems to be a reduction in glutamate release. In contrast, the nonhalogenated inhaled anesthetics (e.g., xenon, nitrous oxide, cyclopropane), as well as the intravenous anesthetic ketamine, have little or no effect on the GABA<sub>A</sub> receptors but depress excitatory glutamatergic synaptic transmission postsynaptically via NMDA glutamate receptor blockade. The study by Dickinson et al. is significant for identifying a shared mechanism by which both xenon and isoflurane inhibit NMDA receptors through competitive antagonism of the binding of the obligatory coagonist glycine, which interacts with a distinct ligand binding site and is required for full receptor activation by glutamate.

Identification of inhaled anesthetic binding sites on putative target proteins has been fraught with difficulty due to the low affinity of the interactions between anesthetic and receptor and the absence of atomic resolution structures of pharmacologically relevant molecular targets. As a result, most atomic resolution anesthetic binding sites have been identified in well-characterized model proteins for which three-dimensional atomic resolution structures are already available. Nevertheless, considerable evidence obtained from molecular modeling and site-directed mutagenesis indicates that the molecular volumes of anesthetic target sites influence modulation of GABA<sub>A</sub> and glycine receptors by these drugs.

This evidence supports the notion that anesthetics modify receptor function by occupying a critical volume within a binding cavity. Internal cavities within proteins are important for conformational flexibility and ligand-induced signal transduction such that occupation of these cavities might alter receptor function. Dickinson et al. took an elegant approach to identify sites of interaction of xenon and isoflurane with the NMDA receptor by combining molecular modeling of xenon binding to the NR1 glycine binding domain with evidence for inhibition of receptor function obtained by patch clamp electrophysiology of heteromeric NMDA receptors consisting of the prevalent NR1/NR2A and NR1/NR2B subunit combinations. Starting with the published crystal structure of the NR1 ligand-binding domain, molecular modeling was used to identify putative xenon binding sites on the NMDA receptor, an innovative approach in the identification of anesthetic receptor interactions. This approach identified a putative xenon binding site that contained up to three xenon atoms and overlapped the known binding site for the coagonist glycine. Moreover, a molecule of isoflurane would fit into this putative xenon binding site. Pharmacologic analysis of recombinant NMDA receptor currents revealed that inhibition by xenon occurred by a mixed competitive/noncompetitive mechanism with glycine, whereas inhibition by isoflurane was competitive with glycine. A point mutation (F639A) in the second transmembrane domain of the NR1 subunit has been shown recently to reduce inhibition by xenon and isoflurane. In support of a glycine competition mechanism, Dickinson et al. showed that the reduced inhibition of NR1(F639A)/NR2A receptors by xenon and isoflurane results from the increased glycine affinity of the mutant receptor and therefore from reduced competition by the anesthetics. These important observations suggest that both anesthetics inhibit NMDA receptors by competing with glycine, the first evidence for direct competitive inhibition of ligand binding to a ligand-gated ion channel by an anesthetic.

Nitrous oxide is also known to inhibit NMDA receptors, and its pharmacologic properties may resemble those of xenon. In view of a recent report that xenon and nitrous oxide share common binding sites within hydrophobic cavities of model proteins considered to be prototypes for the NMDA receptor, it will be interesting to determine whether nitrous oxide interacts with the glycine binding site in a manner similar to that of xenon. Any differences observed between the two anesthetics could be relevant to the neurotoxicity of nitrous oxide compared with the purely neuroprotective effects of xenon.

The identification of binding sites for xenon and isoflurane on the NMDA receptor is an impressive step, but important questions remain regarding the pharmacologic relevance of these findings, particularly with regard to isoflurane. Although NMDA receptor blockade seems likely to mediate the anesthetic and neuroprotective effects of xenon, postsynaptic effects of isoflurane at glutamatergic synapses are relatively minor compared with the presynaptic reduction in glutamate release observed in hippocampal brain slices and isolated nerve terminals. Endogenous neuronal NMDA receptors undergo complex regulation by endogenous agonist and antagonist ligands and ions (e.g., glutamate, glycine, Zn<sup>2+</sup>, Mg<sup>2+</sup>, polyamines), receptor scaffolding and targeting proteins, and multisite phosphorylation, all of which could affect anesthetic sensitivity in vivo. Therefore, pharmacologic effects observed in vitro with cloned receptors expressed in nonneuronal cells must be verified in intact neuronal synapses.

The competitive nature of the xenon and isoflurane effects on glycine indicate that they will have reduced effects in the presence of high extracellular glycine concentrations, in the absence of depolarization sufficient to relieve the voltage-dependent Mg<sup>2+</sup> block of NMDA receptors, and/or with specific receptor subtype combinations. In this regard, the noncompetitive component of the blockade by xenon, which was not observed for isoflurane, might enhance the importance of NMDA block by xenon in both normal and pathologic conditions associated with high agonist concentrations. One of the most important questions that can now be addressed concerns the significance of these interactions
between xenon and isoflurane and the NMDA receptor in terms of the overall pharmacology of these general anesthetics. The solution to this problem should be facilitated by the development of mutant “knock-in” mice expressing the NR1(F639A) point mutation—these mice would be predicted to be resistant to xenon and/or isoflurane anesthesia if this site is important.

The structural information provided by the molecular modeling will facilitate site-directed mutagenesis of the 12 amino acid residues shown to surround the putative anesthetic binding cavity. This will identify residues critical to anesthetic interactions and provide additional evidence for this cavity as a binding site for isoflurane and xenon, and might suggest interesting residues to mutate in vivo. Such evidence is particularly important for isoflurane in the absence of supporting structural or modeling data. Mutations that increase amino acid side chain volume would be predicted to destabilize and ultimately exclude anesthetic binding. These supporting studies should provide further support for this milestone in molecular anesthesiology. In addition to identifying a receptor locale frequented by both noble and nouveau anesthetic gases, Dickinson et al. have identified at atomic resolution a common site of interaction for two dissimilar anesthetics that underlies their shared NMDA receptor blocking effects.

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