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Molecular Approaches to Improving General Anesthetics

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Introduction

Over the last several decades, the average age of patients has steadily increased, while the use of general anesthesia and deep sedation has grown largely outside the operating room environment. Currently available general anesthetic drugs and delivery models represent limitations in addressing these trends. At the same time, research has tremendously expanded our knowledge of how general anesthetics produce their beneficial effects, and also revealed evidence of previously unappreciated general anesthetic toxicities. The goal of this review is to highlight these important developments and describe translational research on new general anesthetic drugs with the potential to improve and reshape clinical care.

1) Demographic and practice trends affecting anesthesiology

Two large trends are affecting demands on anesthesia providers in the United States. The first is the demographic trend toward an aging population, and the second is the increasing utilization of anesthesia for outpatient procedures, frequently outside the traditional operating room environment.

Between 1995 and 2010, the U.S. population over 65 years of age increased by approximately 20%, significantly faster than the total population (1). In the next 15 years, the population aged 65 or greater is expected to increase by over 50% (Table 1). This group of patients has the highest incidence of chronic systemic diseases and also requires more procedures for management of these diseases. Older patients are also over-represented among those undergoing inpatient surgery (2). Moreover, the high frequency of co-morbidities among the elderly population increases their risk for surgical complications and toxicities associated with general anesthesia. Common toxicities of general anesthetics, like hypotension, respiratory depression, and hypothermia, are exaggerated and dangerous in elderly patients. Advanced age is also an important risk factor for post-operative cognitive dysfunction. In summary, anesthetists are confronted with a rapidly increasing population of

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older patients having major procedures as inpatients, and frequently burdened with systemic diseases.

The second trend influencing anesthesia care delivery is the growth in utilization of minimally invasive surgical and diagnostic approaches requiring general anesthesia, but done on an outpatient basis. An assessment by the Agency for Healthcare Research and Quality reported that in 2003, over 50% of surgeries in the U.S. were done on an outpatient basis (2). As the number of ambulatory surgery centers continues to increase, the proportion of outpatient surgeries continues to grow. In these outpatient settings, the risk associated with general anesthesia is frequently greater than that posed by the concomitant procedure; thus, the burden to assure patient safety falls heavily on anesthesia personnel. In addition, recovery from general anesthesia is a particularly critical determinant of surgical productivity in the outpatient setting. For example, colonoscopy exams typically require 20 minutes to complete, but recovery from sedatives frequently given during this procedure often takes an hour or more. Under these conditions, each gastroenterologist requires about three recovery beds and associated equipment and staffing to optimize the number of procedures performed. As a result, faster and more reliable recovery from general anesthesia has the potential to dramatically impact on both efficiency and cost of care in these settings.

2) Mechanisms of general anesthesia

Knowledge about how general anesthetics produce their beneficial and toxic effects is essential as a foundation upon which researchers can design strategies for developing improved anesthetics. The last few decades have seen tremendous advances in our understanding of the mechanisms underlying general anesthesia (3,4).

General anesthetic pharmacology is unique because so many types of molecules possess this activity: simple gases, alcohols, alkanes, ethers, barbiturates, steroids, and other organic compounds. In the 19th century, Claude Bernard asserted that all general anesthetics produced their effects on animals *via* a common pathway (the Unitary Hypothesis), and Meyer and Overton both noted that general anesthetic potency was largely explained by a single biophysical property: hydrophobicity (or lipid solubility). These two seminal ideas led scientists to focus on lipid membranes as the primary site of general anesthetic action. A critical paradigm shift in research on mechanisms of general anesthesia was the change in focus from effects on membrane lipids to direct effects on membrane proteins, and particularly ion channels in neurons. Franks and Lieb (5) demonstrated that the non-specific pharmacology of general anesthetics could be observed in a lipid-free protein enzyme. These experiments showed that lipids were no longer necessary to explain the association between anesthetic drug potency and hydrophobicity, and suggested instead that anesthetics bind directly to sites on proteins. Using molecular biological tools enabling the study of mutated proteins, research on neurotransmitter receptor-channels have provided convincing evidence that general anesthetics do in fact act directly on channel proteins rather than indirectly *via* lipids (6,7).

Major research efforts to identify neuronal ion channels that are likely to mediate the actions of general anesthetics in the central nervous system identified a number of fast neurotransmitter receptor channels, including gamma-amino butyric acid type A ($GABA_A$) receptors, glycine receptors, nicotinic acetylcholine (nACh) receptors, and n-methyl D-aspartate (NMDA) sensistive glutamate channels (3). Other major general anesthetic targets are the two-pore domain potassium (2PK) channels that produce background potassium leaks in neurons, stabilizing them in a non-excitable state (8). Some general anesthetics activate the 2PK channels, further increasing this stabilizing anti-excitatory current.

An important revelation emerged from studies on a variety of ion channel targets: groups of drugs with similar clinical properties often act at similar sets of ion channels (Table 2)(9,10). The important clinical actions produced by all general anesthetics include amnesia, hypnosis (unconsciousness), and immobilization during painful stimuli (11). Other effects, such as analgesia and alterations in autonomic functions, vary widely among different anesthetics. Thus, propofol, etomidate, and alphaxalone are all potent intravenous amnestic/hypnotic drugs, but very high doses are required to prevent movement in response to noxious stimulation. This group of drugs acts primarily by enhancing the activity of inhibitory $GABA_A$ receptors. A group of gaseous general anesthetics including nitrous oxide, xenon, and cyclopropane, are weak immobilizers and hypnotics, but they produce analgesia and autonomic stability. These gaseous agents, along with ketamine, act primarily by inhibiting excitatory ion channels like glutamate and neuronal nACh receptors, but also act at 2PK channels. A third large group of general anesthetics includes the volatile agents and barbiturates. These drugs produce the classic effects of general anesthesia in a predictable manner as their concentration increases: amnesia, then hypnosis, then immobility. Their molecular targets are widespread, including both inhibitory and excitatory neurotransmitter-gated channels, 2PK channels, proteins involved in pre-synaptic neurotransmitter release, and indirect modulators of neuronal excitability such as G-protein coupled receptors.

A small number of sites where general anesthetics interact with ion channels have been identified using photolabeling and mutational analysis. In nicotinic ACh receptors, inhibition appears to be caused by anesthetic binding to a discrete region within the transmembrane cation pore (6). Photolabeling with long-chain alcohols also identified binding sites in the pore domains of nicotinic ACh receptors (12). In $GABA_A$ receptors, a photolabel analog of etomidate was used to identify residues in transmembrane amino acids where two subunits make contact within the membrane (13). Mutations at the photolabeled sites affect interactions with etomidate, confirming that they are likely contact points between protein and drug (14).

In a growing number of cases, transgenic animal studies have strengthened inferences about the role of specific types of ion channels in the actions of general anesthetics. Mice containing $GABA_A$ receptor β 2 or β 3 subunit point mutations that dramatically reduce sensitivity to etomidate, propofol, and volatile anesthetics have proven especially informative. Transgenic mice with a mutation in β 3 subunits display markedly reduced sensitivity to the hypnotic and immobilizing actions of propofol and etomidate, but only modestly reduced sensitivity to isoflurane (15). In contrast, transgenic mice with mutated β 2 subunits show reduced sensitivity to the sedative, but not hypnotic and immobilizing actions of propofol and etomidate (16). These data indicate that $GABA_A$ receptors containing β 3 play a particularly important role in neural pathways mediating major effects of IV anesthetics. Knock-out mice lacking the gene for one anesthetic-sensitive 2PK channel (TASK3) display reduced sensitivity to the actions of specific volatile anesthetics (17). Mutant mice lacking the ε1 subunit of NMDA receptors were shown to be resistant to the hypnotic effects of nitrous oxide (18). However, these knockout mice were also shown to have globally enhanced monoaminergic tone, and their resistance to immobilization by a variety of general anesthetics was sensitive to manipulation of excitatory amino acid levels (19). Related experiments have been done in *C. Elegans*, a flatworm with a simple nervous system. Knockout of the *C. Elegans* gene encoding a homolog of NMDA receptors made animals that were insensitive to nitrous oxide (20). Knockout of another gene encoding a different glutamate receptor channel eliminated sensitivity to xenon (21).

3) General anesthetic toxicities

The toxicities of general anesthetics vary, and the molecular targets underlying toxicities are known in only a few cases. The best understood example is a unique toxicity of etomidate,

the only general anesthetic containing an imidazole group. Suppression of adrenal cortisol synthesis by etomidate was discovered a few years after its introduction into clinical practice (22). The specific molecular target in the adrenal gland was identified as 11β hydroxylase (CYP11B1), a mitochondrial cytochrome enzyme that converts 11-deoxycortisol to cortisol. Given the large number of imidazole derivatives that are known to inhibit various heme-containing enzymes, it is likely that the imidazole ring of etomidate forms a strong coordinate bond with the iron atom in the catalytic center of 11β-hyroxylase, blocking substrate access to this site.

Another unique and rare toxicity is associated with prolonged sedation using propofol; *propofol infusion syndrome*, characterized by dysrhythmias, lipemia, fatty liver, metabolic acidosis, and rhabdomyolysis (23). In this case, it is thought that the toxicity is due not to the anesthetic molecule, but to the lipid component of the drug vehicle, which is used to increase propofol solubility.

Other common toxicities of general anesthetics include respiratory depression, hypotension, hypothermia, and post-operative nausea and vomiting. There is a clear need for investigation of the molecular targets mediating these effects, which likely vary for each type of anesthetic. Some of these targets have been identified for some general anesthetics. For example, anesthetic-sensitive 2PK channels play critical roles in respiratory drive (24) and drugs that selectively inhibit these channels are used as respiratory stimulants (25). Thus, it is likely that anesthetic potentiation of 2PK channel activity contributes to respiratory depression and insensitivity to hypoxia/acidosis. While etomidate and propofol both induce hypnosis and immobility through enhanced $GABA_A$ receptor activation, etomidate produces remarkable hemodynamic stability. It is likely that etomidate lacks activity at target molecules that mediate hypotension in the presence of other anesthetics, but molecular and transgenic animal studies also suggest that hemodynamic stability with etomidate is due to its agonist activity at certain adrenergic receptors (26). Similarly, propofol is widely favored as an induction agent for general anesthesia because it produces less postoperative nausea and vomiting than other related drugs. While the molecular targets triggering PONV by other anesthetics are not well defined, there is evidence that propofol possesses a unique anti-emetic activity, apparently mediated indirectly through cannabinoid receptors (27).

In addition to the short-term toxicities noted above, evidence of potential long-term neurotoxic effects of general anesthetics is a source of growing concern for patients and physicians (28). Post-operative cognitive dysfunction (POCD) is a transient cognitive impairment characterized by problems with memory, concentration, language comprehension, and social integration (29). It usually resolves within one year, but is also associated with an increased risk of dementia developing years later (30). Known risk factors for POCD include advanced age, low educational background, chronic diabetes and/or vascular disease, and CAGB surgery (31,32). Notably, many of these symptoms and risk factors for POCD are similar to those for Alzheimer's Disease, a common form of dementia in the elderly. Preclinical models of POCD suggest that the type of anesthesia may be an important pathogenic factor as well (33,34), although clinical studies have not consistently supported this hypothesis (35). Nonetheless, evidence is accumulating that general anesthetics cause long-term changes to neuronal viability and function. In particular, volatile anesthetics have been shown to accelerate the oligomerization of A-beta (Aβ) peptide, which is though to be an early step in the development of Alzheimer's dementia (36). Neurons exposed to both Aβ and volatile anesthetics undergo cell-death at a significantly higher rate than those exposed to Aβ alone. Another hypothesized mechanism for POCD suggests that it is caused by increased systemic inflammation associated with surgery, and perhaps enhanced by certain general anesthetic drugs (37). Surgery and anesthesia increase the release of a number of inflammatory mediators, including tumor necrosis factor alpha

(TNFα), tissue growth factor beta (TGF-β) and pro-inflammatory interleukins (IL-1β and IL-6). Again, clinical evidence does not strongly support this hypothesis (38), but it is likely that POCD is multifactorial.

At the other extreme of age, concern is growing that general anesthetics may be harmful to the developing brain. There is convincing evidence that most known general anesthetics dramatically accelerate neuronal apoptosis (cell death) during critical phases of fetal brain development in both rodents and primates (39,40). Rodent experiments also suggest that this damage can lead to abnormal learning and memory functions, although evidence of these manifestations in humans remains controversial while definitive studies are conducted. Mechanisms underlying this toxicity appear to be linked to the same ion channels that mediate the beneficial effects of general anesthesia. For example, a wide variety of general anesthetics that enhance $GABA_A$ receptor activity are hypothesized to produce excito-toxicity in developing neurons, which have different transmembrane chloride gradients than mature neurons. Interestingly, ketamine lacks $GABA_A$ activity, yet also produces neuro-apoptosis in developing animal brains (41,42).

4) Strategies for developing new general anesthetics

The issues reviewed above represent a multi-dimensional framework for improving upon existing general anesthetic drugs. The ideal general anesthetic would address all of these issues (List 1), but in the real world, drug development efforts are often limited to a small number of goals. Broadly speaking, these efforts are aimed at a) ameliorating the neurotoxic effects of current general anesthetics, b) reducing or eliminating other clinically significant toxicities of specific agents through mechanism-based drug design, and c) identifying novel general anesthetic compounds.

Neuroprotection Strategies—*Xenon* is a mono-atomic noble gas. It possesses anesthetic activity, and as an anesthetic, displays many attractive features (43). It is odorless and non-pungent, and produces no bronchial reactivity during inhalation. Xenon solubility in blood and tissue is lower than that of nitrous oxide, and it therefore has even faster onset and offset kinetics. It is stable in storage, non-flammable, undergoes zero metabolism, elicits no allergies, and produces minimal cardiovascular depression. Xenon itself is environmentally benign, although the amount of energy required to collect and purify it represents a considerable, albeit indirect, environmental impact. Toxicities of xenon include respiratory depression, hypothermia, and PONV. In addition, MAC for xenon is 0.6 atm, and its use at high partial pressures is associated with expansion of trapped air spaces in the body. The major impediment to xenon as a clinical anesthetic is its cost (over $10/litre), which currently is prohibitive, but technologies to enable closed-circuit administration and reclamation of xenon in scavenged gas may reduce the overall cost of this anesthetic.

A research team at Imperial College in London has renewed clinical interest in xenon as an anesthetic with unique neuroprotective properties. Their research in preclinical models has shown that xenon protects neurons and brain tissue from damage caused by anoxia (44), cardiopulmonary bypass (45), traumatic brain injury (46), or volatile anesthetics in developing brain models (47). Mechanistic studies demonstrate that xenon inhibits NMDA receptors, and molecular modeling suggests that unlike other drugs with similar activity, xenon may bind within the glycine co-agonist sites of these proteins (48).

Two clinical trials focusing on acute POCD have so far demonstrated no protective effect with xenon (49,50). Two other clinical trials are investigating neuroprotection by xenon; one in the setting of brain ischemia in cardiac arrest and another in the setting of perinatal asphyxia.

Alternative neuroprotective strategies focus on compounds that lack anesthetic activity. ***Argon***, like xenon, appears to have some neuroprotective activity in preclinical models (51). In addition, ***inhibitors of inflammatory mediators*** like TNFα are also being investigated for their perioperative organ protective properties.

Mechanism-based drug design—A detailed understanding of mechanisms underlying both beneficial and toxic anesthetic actions enables researchers to identify ways that these actions can be independently manipulated. An excellent example is the development of the water soluble propofol pro-drug, ***fospropofol***, eliminating both the need for lipid carrier and reducing the risk of propofol infusion syndrome (52). Because of recently discovered problems with the assay used for fospropofol, the validity of clinical pharmacokinetic and pharmacodynamic studies, and their comparison with propofol, is questionable and a number of these studies have recently been retracted (53). Nonetheless, this formulation may have clear advantages over propofol for long-term sedation.

A team at Harvard (of which this author is a member) has recently applied mechanism-based drug design in the development of two new etomidate analogs. Both of these new compounds have the potential to reduce adrenal toxicity. ***MOC-etomidate*** is a "soft" etomidate analog (54). Like esmolol and remifentanil, MOC-etomidate incorporates an accessible ester linkage, imparting rapid metabolism by non-specific esterases in blood and tissues. Because it is metabolized at least 100 times faster than etomidate, MOC-etomidate is associated with a much shorter period of adrenal suppression. Assuming it can be utilized as an infusible general anesthetic for procedures of modest duration, MOC-etomidate may also provide for reliable rapid emergence. ***Carbo-etomidate*** is another etomidate analog designed to retain the molecular shape of the parent drug, while eliminating its adrenal toxicity (55). This was achieved by replacing the 5-membered imidazole ring of etomidate with a pyrrhole ring, placing a carbon in the position of the nitrogen that was implicated in heme binding interactions. Carboetomidate shows potent hypnotic activity in animals, and appears to maintain other favorable clinical attributes of etomidate. In addition, its potency for inhibition of 11β-hydroxylase is approximately 1000-fold lower than that of etomidate.

Screening for new general anesthetics—While the strategies described above rely on exploitation of existing knowledge, the value of improving general anesthetics may have reached a tipping point where high-risk exploration strategies are justifiable. A research team at University of Pennsylvania has combined two recent discoveries to launch such an effort. The first advance was the identification of a soluble protein that binds a wide variety of general anesthetics with high affinities. ***Apoferritin*** is a 24-subunit globular protein that binds and transports iron in all cells and tissues. Interestingly, ferritin subunits each contain four helical domains, a structure similar to the four transmembrane helices of $GABA_A$ receptor subunits. The team at Penn discovered that apoferritin binds a variety of volatile anesthetics and propofol analogs with affinities that correlate nicely with the ability to potentiate GABA responses at $GABA_A$ receptors (56,57). Furthermore, crystallographic studies showed that the anesthetic binding pocket in apoferritin is formed by helical domains at the interfaces between subunits, echoing the structure of anesthetic sites in $GABA_A$ receptors. The Penn team also discovered a ***fluorescent general anesthetic, 1-aminoanthracene***, which binds selectively to neural tissues, and also to apoferritin (58). These two technologies were combined to create a high-throughput screening tool that uses fluorescence to detect novel compounds that compete with 1-aminoanthracene for occupation of the anesthetic site on apoferritin (59). The initial screen identified 18 new compounds that are being further tested for general anesthetic activity.

Summary

A variety of emerging factors are challenging anesthetists to improve safety, productivity, and the overall quality of patient experience. These include 1) a rapidly growing population of elderly patients, who have a high incidence of significant coexisting systemic diseases, and who are likely to undergo a growing number of major surgical procedures as inpatients; 2) rapidly expanding utilization of outpatient diagnostic and therapeutic procedures requiring general anesthesia and rapid recovery; and 3) growing concern about long-term impact of general anesthesia on the brain and its functions, particularly POCD in the elderly and accelerated neuronal death in fetal development. Basic research during the last two decades has revealed a great deal about both mechanisms of general anesthesia and likely mechanisms of anesthetic toxicity. This knowledge is now being exploited in research projects aimed at meeting some of the clinical challenges ahead of us. Anesthetics such as xenon, which possess neuroprotective activity, are being re-evaluated in clinical trials. We should soon know whether benefit to patients at high risk for brain dysfunction following surgery and anesthesia will justify the high cost of xenon. Mechanism-based drug design has resulted in development of fospropofol, a water-soluble pro-drug that eliminates the risk of devastating toxicity associated with long-term propofol infusion. Related strategies have been applied in development of two new etomidate derivatives. MOC-etomidate was developed based on a pharmacokinetic strategy, providing rapid metabolism by non-specific esterases that promises to both reduce the duration of adrenal toxicity, and to provide more predictable/reliable recovery from general anesthesia. Carboetomidate used a pharmacodynamic strategy to selectively eliminate etomidate toxicity, while retaining its beneficial clinical features. Finally, the need for improved general anesthetics has fostered a search for new drugs. This high-risk approach may eventually lead to discovery of entire new classes of general anesthetic compounds that may provide additional benefits to our patients.

List 1 Characteristics of an Ideal General Anesthetic Drug

- Safety—high therapeutic index and no toxicities (perhaps even organ protective).
- Comfort—minimal pain on injection or minimal pungency if inhaled.
- Rapid onset/offset.
- Low metabolic burden and safe in renal/hepatic dysfunction (potent if IV, non-metabolized if inhaled).
- Economical to make and store.
- Environmentally benign.

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Table 1

Growth in Elderly United States Population

Year	Estimated U.S. Population	% Age ≥ 65 yr	Population ≥ 65 yr
1995	265,066,000	12.8	33,928,000
2010	309,163,000	13.2	40,810,000
2025	337,361,000	18.5	62,412,000

Data are based on United States Population Projections published by the Census Bureau (1)[Campbell PR: Population Projections for States by Age, Sex, Race, and Hispanic Origin: 1995 to 2025. U.S. Bureau of the Census, Population Division, 1996. PPL-47, 90 pages].

Table 2

Correlation Between Clinical Profile and Molecular Targets of General Anesthetics

	Group 1	Group 2	Group 3
Drugs	Etomidate, Propofol, Alphaxalone	Barbiturates Halogenated Alkanes & Ethers	Nitrous Oxide, Xenon, Ketamine, Cyclopropane
Ratio of MAC-Immobility : MAC-Hypnosis	4+	2–3	1.5–2
Analgesia	None	None	Yes
Organ Protection	None	Ischemic Preconditioning	Yes (xenon)
EEG effects	Reduced Frequency	Reduced Frequency	Minimal change or increased frequency
Molecular Targets	$GABA_A$ receptors HCN1 (propofol)	$GABA_A$ receptors, Glycine receptors Neuronal nAChRs 2PK channels Glutamate Receptors Others	Glutamate receptors Neuronal nAChRs 2PK channels Others