The Future of Anesthetic Pharmacology

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There have been few, if any, significant new drugs introduced into the practice of Anesthesiology in the last 10 yr. Look at when the FDA approved our "new" drugs:

- Desflurane → 1992
- Mivacurium → 1992
- Rocuronium → 1994
- Cisatracurium → 1995
- Sevoflurane → 1995
- Remifentanil → 1996
- Dexmedetomidine → 1999
- Since then → Nothing!

This lack of progress does not reflect that we lack unmet medical needs. If we examine the three classes of drugs typically associated with anesthesia practice, we find significant problems with the present armamentarium.

There are numerous problems with the available hypnotics. The inhaled anesthetics, as a class, appear to be pronociceptive at low concentrations (1–3), potentially increasing postoperative pain. Propofol stings on injection, despite the various tricks used to attenuate this brief, but intense, pain (4,5). Propofol infusions are associated with acidosis and multiorgan failure in children (6) and occasionally in adults (7). Thiopental is unsuitable for maintenance due to accumulation. Etomidate for induction causes myoclonus, and maintenance of anesthesia results in adrenal suppression (8,9).

Our available analgesics are limited to opioids, ketamine, and NSAIDS. The opioids share the common side effects of ventilatory depression, ileus, sedation, pruritis, urinary retention, and addictive potential. Ketamine causes psychosis. The nonselective NSAIDS are associated with increased risk of bleeding and may delay bone healing, while the COX-2 selective NSAIDS are prothrombotic (10).

As to muscle relaxants, we still do not have a replacement for succinylcholine. Rapacuronium showed promise when it was approved in 1999, but it lasted on the market for less than a year, because it causes severe bronchoconstriction (11) by an unusual action on M3 muscarinic receptors (12). In fact, the last exciting development in muscle relaxants was when vecuronium went generic in 1995.

The good news is that we are not an orphaned specialty. There are exciting, new pharmaceuticals in the pipeline that may profoundly change the practice of anesthesia over the next decade. I will quickly summarize information that is publicly available about these. By way of disclosure, I have consulted to Alza, Amphastar, AstraZeneca, Delex, Durect, Endo, Glaxo, Guilford, Painceptor, and Theravance, whose products are mentioned below.

HYPNOTICS

A number of companies are working on alternative formulations for propofol (13). The primary goals are to remove or alter the lipid, which may be associated with propofol syndrome. The "Diprivan" formulation of propofol, the original product from AstraZeneca, is a mixture of propofol in Intralipid, a mixture of long-chain triglycerides. Intralipid may cause dysfunction of the reticuloendothelial system (14,15). Additionally, the pain on injection with propofol is associated with the free fraction (16,17), and modifications of the formulation can potentially reduce the free propofol concentration (18).

The Braun Corporation introduced the "Lipuro" formulation emulsifying propofol in medium- and long-chain triglycerides. The Lipuro formulation does not alter the pharmacokinetics of propofol (16), but it is associated with less pain on injection (19,20). Triglyceride chain length influences how triglycerides affect the immune system (21), and the medium-chain triglyceride formulations have been shown to be beneficial *in vitro* (22). However, I could not find any studies suggesting that use of the medium-chain formulation of propofol had any beneficial effects on the immune system when compared with the original Diprivan formulation.

Another medium-chain triglyceride propofol formulation is IDD-D propofol, developed by RTP Pharma, a Canadian company. This is a 2% formulation, twice the concentration of propofol found in Diprivan. Although it reduces the lipid load (as would be expected, since it is twice as much propofol per milliliter of lipid vehicle) (23), it is associated with increased pain on injection and, interestingly, a slower onset of drug effect than Diprivan (24). Increased pain on injection has also been reported for the "Ampofol" low-fat propofol formulation developed by Amphastar (25,26).

Cyclodextrins are water-soluble cyclic carbohydrates. As shown in Figure 1 [from Ref. (13)], they contain a hydrophobic cavity that can accommodate a lipid-soluble drug molecule (27). Egan and colleagues

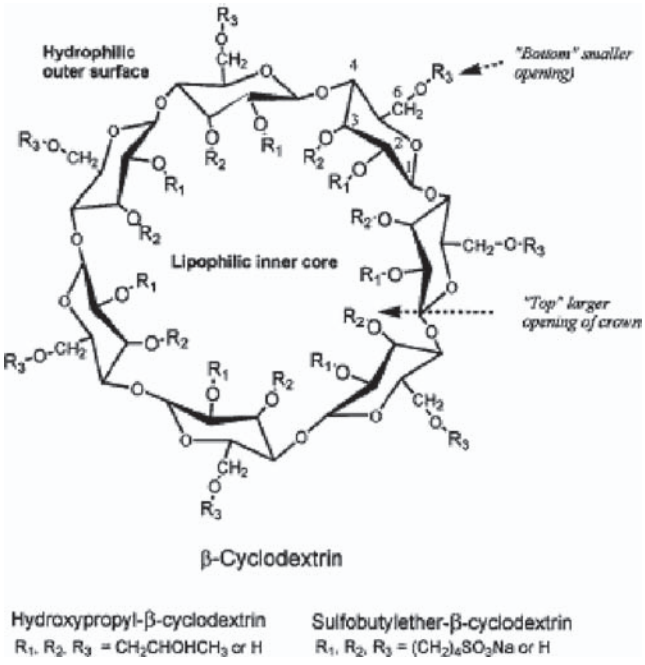

Figure 1. Cyclodextrins, water-soluble cyclic carbohydrates, contain a hydrophobic cavity that can accommodate a lipid-soluble drug molecule. From Baker and Naguib (13).

documented equivalent propofol pharmacokinetics and pharmacodynamics with a sulfobutyl ether-β-cyclodextrin and Diprivan (28,29).

Another option being explored for propofol delivery is micelles, as shown in Figure 2 [from Ref. (13)]. These micelles are small, which makes formulations of propofol in micelles visually clear (30). Maelor, a UK

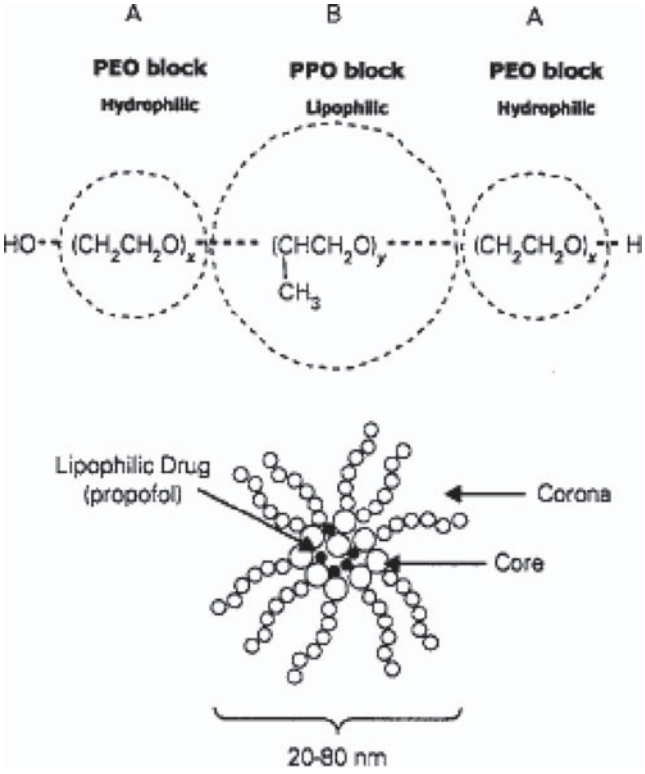

Figure 2. Micelles. From Baker and Naguib (13).

pharmaceutical company, has developed a micellar formulation of propofol (http://www.maelor.plc.uk/) that is apparently associated with increased pain on injection (http://www.maelor.plc.uk/pdfs/products/poster.pdf). A clear formulation of propofol, Cleofol, has recently been introduced in India by Themis Medicare. The clear appearance suggests that the propofol is emulsified in micelles, although the manufacturer has not disclosed the preparation. This formulation is associated with an 89% incidence of severe pain on injection (31), as well as damage to infusion sets (32) and veins (33). In fact, this formulation is so problematic that one group of investigators concluded that the Cleofol propofol formulation "should only be used for patients who demand a pure vegetarian induction agent" (34).

Lastly, Guilford Pharmaceuticals has been pursuing development of water-soluble prodrug of propofol, termed "Aquavan" (35,36); as shown in Figure 3 [from Ref. (37)], Aquavan is a phosphate-linked propofol prodrug that, upon hydrolysis, releases phosphate and formaldehyde. The propofol concentration peaks approximately 8 min after an injection of Aquavan (37). Almost all subjects receiving Aquavan report a paresthesia on injection (37), which has been described as "a transient unpleasant sensation of burning or tingling of moderate severity in the anal and genital region" (38). The slow onset of sedation with Aquavan renders it unsuitable to replace propofol as an anesthetic induction agent. Aquavan is now being developed by MGI Pharma for procedural sedation (http://www.mgipharma.com/wt/page/aquavan).

A truly novel hypnotic is currently in development at Theravance Corporation. This compound has been described only in abstracts (39–41). Figure 4 shows the offset of drug effect in rats following Diprivan infusions of 20 min, 3 h, and 7 h, and THRX-918661. No available data suggests that this drug has advanced to clinical trials, but a hypnotic with ultrarapid metabolism could revolutionize anesthetic practice as much as Diprivan did 20 yr ago.

Xenon continues to be explored for its hypnotic properties, and a company, Protexeon, is currently developing Xenon for commercial use (42). Xenon has potent analgesic properties (43,44). However, much of the current interest in Xenon is based on its neuroprotective properties (45–47). Xenon has been shown to produce more rapid recovery than isoflurane, with a favorable cardiovascular and respiratory profile (48). The primary obstacle towards use of Xenon is the high cost, estimated to be approximately $160 for a 4-h anesthetic (49). The cost is not astronomical, given that Xenon comes close to being an "ideal" inhaled anesthetic, but to date the cost has precluded any company from bringing Xenon to the market.

Melatonin and melatonin analogs possess hypnotic properties when injected IV, comparable to the properties of propofol and thiopental, at least in rats (50). The EEG effects of IV melatonin resemble the effects of thiopental and propofol (51). The melatonin analog

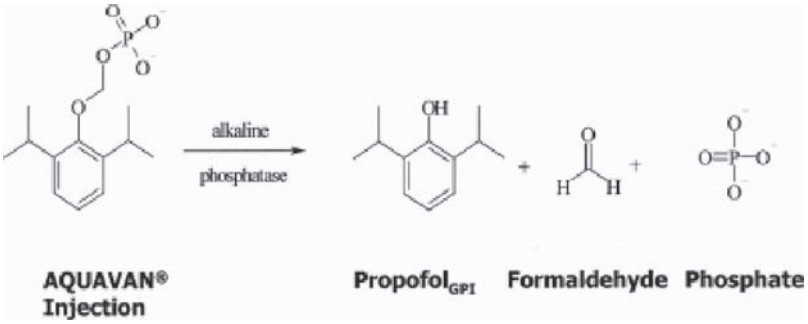

Figure 3. Aquavan, a water-soluble prodrug of propofol. From Gibiansky et al. (37).

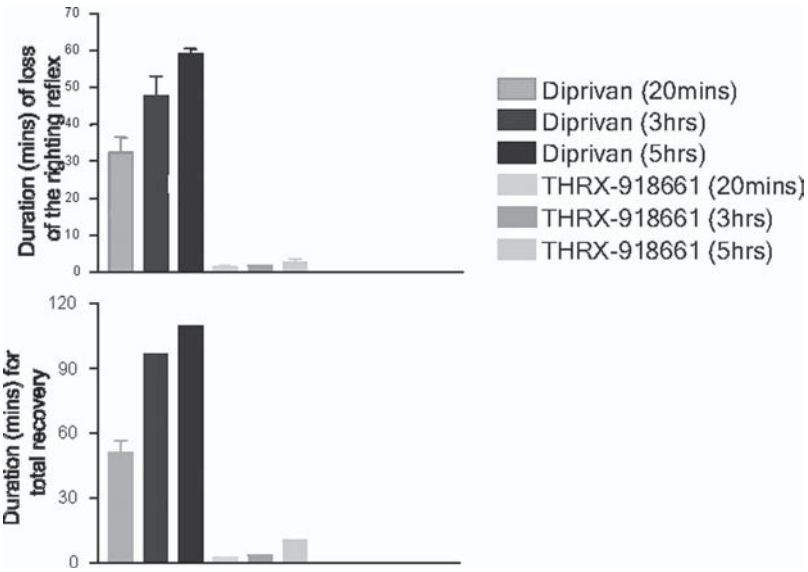

Figure 4. Offset of drug effect in rats after Diprivan infusions of 20 min, 3 h, and 7 h (left bars), and THRX-918661 (right bars). From Beattie et al. (39).

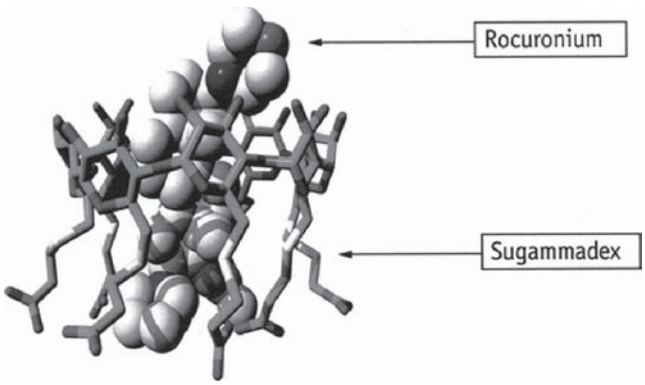

Figure 5. Sugammadex has a pocket that specifically binds rocuronium. From Sorgenfrei et al. (55).

2-bromomelatonin is more potent than melatonin. It also renders rats unconscious, with rapid onset and recovery, similar to that observed with propofol (52). Low concentrations of 2-bromomelatonin also appear to be analgesic in rats, unlike propofol which has no analgesic properties. Melatonin anesthesia is apparently reversible with flumazenil (53). To date no human data exist on the use of melatonin to induce or maintain anesthesia.

MUSCLE RELAXANTS

The most exciting development in muscle relaxants is the imminent introduction of sugammadex, a name as novel as the compound. Sugammadex is a cyclodextrin specifically designed to bind rocuronium (54). As shown in Figure 5 [from Ref. (55)], Sugammadex has a pocket that specifically binds rocuronium (56). By binding the available rocuronium, sugammadex rapidly and completely reverses neuromuscular blockade, even in the presence of an ongoing infusion of rocuronium. In human studies, sugammadex 8.0 mg/kg reversed neuromuscular blockade within 1 min of administration, without any apparent toxicity (55,57). If sugammadex does not have some as-yet unappreciated toxicity, it will render conventional pharmacological reversal of neuromuscular blockade obsolete. Patients will no longer be exposed to the nausea-inducing properties of neostigmine, or the tachycardic effects of atropine and glycopyrrolate. Additionally, imperfect titration of a muscle relaxant occasionally creates a block that cannot be readily reversed at the conclusion of anesthesia. This will no longer be an issue with sugammadex, as even profound neuromuscular blockade can be readily reversed by giving an adequate dose of sugammadex.

The drug to the shown in Figure 6 [from Ref. (58)] is GW280430A, an asymmetric mixed-onium chlorofumarate, currently under development by GlaxoSmithKline (58,59). This is a novel structure for a muscle relaxant, although it has many similarities to mivacurium. GW280430A undergoes metabolism in

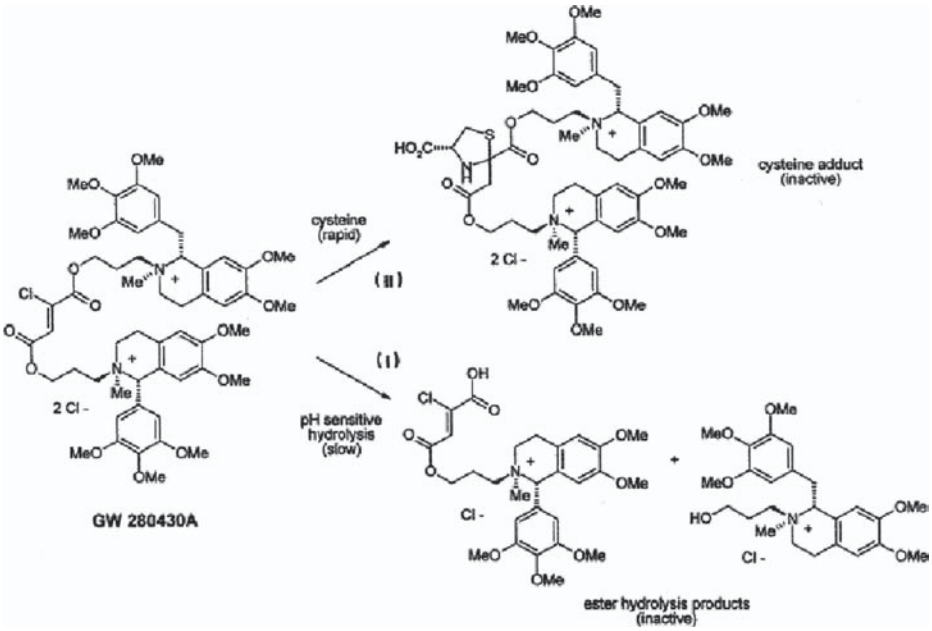

Figure 6. GW280430A, and asymmetric mixed-onium chlorofumarates. From Savarese et al. (58).

the plasma by alkaline hydrolysis and, apparently more significantly, spontaneous formation of cysteine adducts, deactivating the molecule (60). Since this is a spontaneous reaction in blood, it does not depend on any catalytic activity, and thus should be associated with very little genetic variability in the population.

The onset GW280430A is only slightly slower than succinylcholine. In human studies, peak effect at a dose of 0.18 mg/kg (ED_{95}) ranges from 2.3 to 3 min, with recovery in approximately 10 min (61). Increasing the dose to 0.54 mg/kg (three times the ED_{95}) hastens the onset time to 1.2 to 1.8 min, and increases block duration to approximately 15 min. Higher doses cause the release of histamine, similar to mivacurium, without significantly enhancing the rate of onset. GW280430A comes the closest to a true succinylcholine replacement of any nondepolarizing muscle relaxant to date.

ANALGESICS

Analgesics are perhaps the most exciting area of pharmaceutical development related to the practice of anesthesia. This review will cover new developments in opioid pharmacology, followed by other centrally acting analgesics, and conclude with peripherally acting analgesics.

Opioids

Perhaps the most remarkable change in analgesics in the past 10 yr has been the morphing of fentanyl from an esoteric IV analgesic exclusively used by anesthesiologists to a drug commonly used for many kinds of chronic pain. This has been accomplished through the introduction of transdermal fentanyl for cancer pain, and the subsequent introduction of oral transmucosal fentanyl citrate for "breakthrough pain" in cancer patients. Duragesic sales were 1.2 billion dollars in 2004, making it one of the most commercially successful analgesics ever introduced. Actiq sales in 2005 were expected to exceed 400 million dollars. Cephalon, the company that sells Actiq, is now working on a rapidly dissolving sublingual fentanyl tablet called "Oravescent," which provides more rapid onset than the oral transmucosal fentanyl delivery system (61).

Pharmaceutical companies continue to innovate with fentanyl delivery systems. Alza recently received approval for "E-trans" fentanyl, a transdermal iontophoretic fentanyl delivery system. As shown in Figure 7, pain relief with the E-trans fentanyl delivery system was comparable to that of PCA morphine for postoperative analgesia (62).

Another route of fentanyl delivery is through the lungs. Inhaled free fentanyl has a rapid peak and offset, resembling IV administered fentanyl (63). However, the rate of onset and the duration of effect can be modulated by encapsulating inhaled fentanyl in liposomes (64), an approach being explored by Delex pharmaceuticals.

Sufentanil is also being adapted to the needs of patients with chronic pain. Durect, an Alza spin-off, is developing a system to deliver systemic sufentanil over a period of months with an injectable osmotic pump (65). The device, shown in Figure 8, is approximately the size of a matchstick. Because sufentanil is highly potent, this one device can potentially delivery 3 to 6 months of sufentanil to a patient with chronic, unrelenting pain.

Morphine is another old analgesic that has been reintroduced recently with a novel delivery system. In 2004 Endo Pharmaceutical introduced "DepoDur," epidural morphine in a liposomal formulation. A single epidural injection provides up to 2 days of effective analgesia after hip replacement surgery (66).

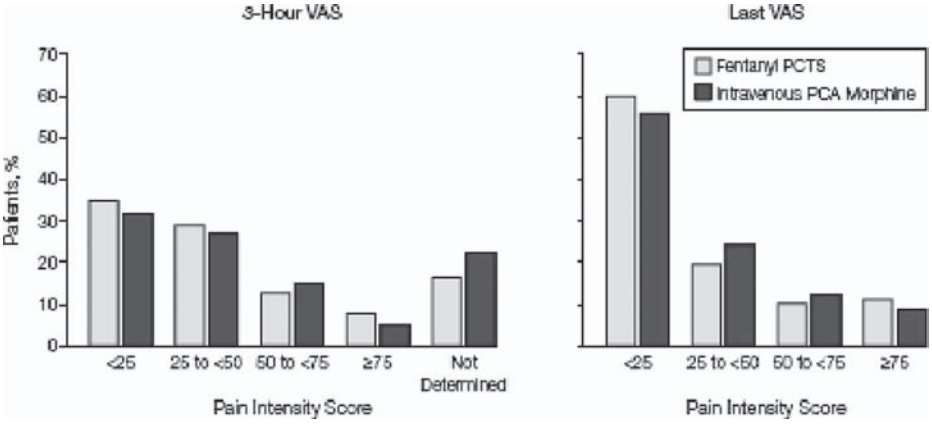

Figure 7. Pain relief with the E-trans fentanyl delivery system was comparable to that of patient-controlled analgesia (PCA) morphine for postoperative analgesia. From Viscusi et al. (62).

Figure 8. Injectable osmotic pump developed by Durect to deliver systemic sufentanil over a period of months. From www.durect.com.

This formulation of extended-release morphine has also proven effective following Cesarean delivery (67) and abdominal surgery (68).

Morphine-6-glucuronide is another "old" analgesic. However, this active metabolite of morphine has never been introduced into clinical practice. Nevertheless, it is currently being developed for postoperative analgesia by CeNeS Pharmaceuticals. Studies suggest that morphine-6-glucuronide causes less ventilatory depression per an equipotent analgesic dose than morphine in human volunteers (69). It may also have activity in peripheral antinociception (70).

Lastly, there are exciting developments in drugs that antagonize opioid side effects. Two drugs are very near FDA approval, alvimopan from Adolor, and methylnaltrexone from Progenics. Alvimpan, the "Molecule of the Month" in June 2005 (71), is an orally delivered μ opioid antagonist to prevent opioid-induced ileus (72). It has very little systemic absorption, and it does not cross the blood-brain barrier. It effectively reverses opioid-induced ileus (73). Methylnaltrexone is absorbed systemically following oral delivery, but does not cross the blood-brain barrier. It is being developed for oral, IV, and subcutaneous delivery. It also effectively reverses ileus, and it is exceedingly well tolerated (74).

In a landmark study, Manzke (an anesthesiology resident at the time) and colleagues identified that role of $5HT_{4(a)}$ agonists on opioid-induced ventilatory depression (75). Specifically, a Novartis $5HT_{4(a)}$ agonist, BIMU8, selectively reversed fentanyl-induced ventilatory depression, without affecting analgesic response in rats. This creates the possibility that opioids could be co-formulated with $5HT_{4(a)}$ agonists, preventing opioid-induced ventilatory depression.

Other Centrally Acting Analgesics

Melatonin possesses analgesic activity that is reversed by naloxone (76). Recent studies suggest that the analgesic activity of melatonin is related to the release of β-endorphin (77). Melatonin also has anti-inflammatory properties that may contribute to its analgesic effects (78).

Cannabinoids are also a potentially important new class of analgesics. Dronabinol is a synthetic δ-9-tetrahydrocannabinol that has demonstrated analgesia in patients with multiple sclerosis (79). However, the use of dronabinol is limited by dizziness and other central effects. Ajulemic acid is a novel cannabinoid with no psychotropic effects (80). It has been shown to be effective in chronic neuropathic pain (81,82).

Peripherally Acting Analgesics

Peripheral kappa opioid agonists continue to be pursued as analgesic targets (83). There is evidence that peripheral kappa agonists can be effective analgesics (84,85).

Many peripheral opioids act through the "Transient Receptor Potential V1" (aka VR1 and TRPV1) ion channel. This channel, located mostly on C fibers in the periphery, is sensitive to capsaicin, acid, heat, and some lipids. Opening this channel permits the influx of calcium, triggering an action potential.

Calcium is toxic to C fibers in high doses. Capsaicin can hold this channel open long enough to permit enough calcium to enter to cause the C fiber to become nonfunctional. This is the basis of capsaicin use for chronic pain (86). Resiniferatoxin permits enough calcium to enter that the C fiber is permanently destroyed, providing long-term analgesia through selective chemical ablation of C fibers (87–89). Resiniferatoxin is another potentially revolutionary development in anesthetic pharmacology, particularly in the treatment of severe chronic pain in terminally ill patients.

Acid causes pain both through TRPV1 receptors as well as through specific, acid-sensing ion channels (90). The "ASIC" channels blocked by the diuretic amiloride are promising candidates for analgesic development (91). Painceptor, a Canadian company, currently has identified candidate ASIC antagonists (http://www.painceptor.com/page.asp?intNodeID = 15188).

CONCLUSION

To conclude, after a decade of relatively sparse pharmaceutical industry interest in anesthetic drugs, we are now posed to dramatic developments in the three major classes of drugs primarily associated with our specialty: hypnotics, muscle relaxants, and analgesics. Of these, the analgesic pipeline has the most candidates, and it addresses the largest unmet medical need of our specialty.

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