Local Anesthetics: Basic Mechanisms and Clinical Implications

Charles B. Berde, M.D. Ph.D. **Boston, Massachusetts**

Overview: The focus of the lecture is "how better understanding of local anesthetic mechanisms can improve current and future clinical uses of these agents for regional anesthesia and analgesia".

1. Recent Research on Ion Channels and Local Anesthetic Mechanisms

a. Actions on sodium channels. Local anesthetics inhibit flux of sodium ions through voltage-gated sodium channels and block impulse propagation. The Modulated Receptor Hypothesis emphasizes the higher binding affinity of local anesthetics for open and inactive Na+ channels compared to resting Na+ channels (Figure 1). Differential binding to channels in different conformations may underlie use-dependent blockade: block intensifies with higher rates of nerve stimulation(1). Local anesthetics have multiple molecular and cellular actions, including: (a) blockade of calcium and potassium (2,3) (4)channels and NMDA receptors(5), (b) impairment of axoplasmic transport (c) blockade of transduction of mechanical stimuli in nociceptors(6) (d) anti-inflammatory (7), anti-thrombotic, and microvascular effects (8) and (e) neuronal(9) and myocyte (10) injury. Anti-inflammatory effects of local anesthetics involve local, contralateral, systemic, and segmental spinal actions(11,12).

b. Local anesthetic uptake and distribution into nerve. Tissue barriers limit local anesthetic potency and effectiveness by impairing passage of drug from extraneural sites into nerve. The simplified diagram in Figure 2 emphasizes that for local anesthetics, unlike most systemically acting drugs, uptake from injection sites into the central circulation takes drug away from, rather than towards, effect sites, and the central circulation is in parallel with, rather than in series with, the path from administration site to effect site. Less than 2% of an injected dose in peripheral nerve blocks enters the nerve. (13) Changes in local blood flow (14) and permeability can dramatically modify local anesthetic potency and duration. The requirement for high solubility and rapid diffusion in both aqueous and lipophilic environments is a major physical-chemical constraint limiting development of new local anesthetics.

c. Local anesthetics are extremely useful Local anesthetic-based analgesic approaches, both neuraxial and peripheral, are essential components of a multimodal approach to postoperative recovery that permits early mobilization and minimizes postoperative disability (15) (16) . Systemically-administered local anesthetics are useful analgesics for neuropathic pain. In some patients and in animal models, the duration of pain relief from intravenous lidocaine far outlasts the duration of therapeutic drug concentrations in plasma (17). Multiple sites of action underlie systemic lidocaine's efficacy in neuropathic pain (18). Lidocaine suppressed ectopic discharges in rat dorsal root ganglia and at peripheral sites of nerve injury at very low doses (19). Lidocaine reduces c-fiber-evoked activity in isolated rat spinal cord via reductions in NMDA and neurokinin receptor-mediated post-synaptic depolarizations. (20) Mexiletine's utility is limited by gastrointestinal and CNS side-effects. Systemic lidocaine may have a role for prevention and treatment of postoperative pain(21) and for selected patients with opioid-refractory pain in palliative care (22). Regional anesthesia and analgesia may modulate development of neuropathic pain in some clinical settings and in some animal models (23); controversy persists regarding factors that impact on effectiveness.

2. Current-generation local anesthetics produce systemic and local toxicities

a. Local anesthetic cardiotoxicity and CNS toxicity (especially seizures) continue to cause cardiac arrests, neurologic injuries, and deaths on a regular basis. Epidemiologic information on systemic complications is sparse and largely retrospective (24). Pediatric data are available from two prospective studies of regional anesthesia in France and other French-speaking countries (25) (26), and from a report of a pediatric cardiac arrest registry (27) . In a registry from Japan, local anesthetic toxicity accounted for only a small fraction of cardiac arrests occurring in association with regional anesthesia(28). Local anesthetic toxicity can cause morbidity and mortality when used by the "tumescent" technique in plastic surgical procedures, such as liposuction, particularly when recommended doses are exceeded. Mortality estimates for liposuction have ranged as high as 1:5,000 procedures (29). Multiple factors reduce the systemic safety margin for local anesthetics and regional anesthesia in infants, compared with adults(30) . Chloroprocaine is unique among available agents in that its clearance by plasma esterases is extremely rapid, even in preterm neonates(31,32). This feature makes chloroprocaine uniquely suited for epidural infusions in neonates.

b. Methemoglobinemia – A recent FDA advisory cited cases of clinically significant methemoglobinemia following topical use of benzocaine, particularly with mucosal administration(33).

c. Local anesthetics produce concentration-dependent local tissue toxicity in nerves (34) and muscles(10).

3. Local Anesthetic Failure: Inflammation, Infection, Tachyphylaxis, Hyperalgesia, Neuropathic Pain, and Genetics Local anesthetics frequently fail to provide analgesia in sites of infection or inflammation. This is a substantial problem in dentistry – in the setting of a tooth abscess or severe pulpitis, failure rates of local anesthesia may exceed 70%. Both PK versus PD mechanisms (including activation of peripheral excitatory amino acid receptors) may be involved in inflammation-induced local anesthetic failure(35,36) . Repeated or prolonged administration of local anesthetics can fail due to tachyphylaxis, which may involve PK (37)and more prominently PD (38-40) (41) mechanisms related to hyperalgesia (38) (42) . Co-administration of systemic or neuraxial opioids with local anesthetics in epidural infusions slows development of tachyphylaxis (43). In a rat model, tachyphylaxis was associated with hyperalgesia, and was prevented by blockade of NMDA receptors or via blockade of NO synthase (38-40). Rotation among local anesthetics was helpful in a study of intrathecal infusions for advanced cancer. (44) Occasional patients report that "local anesthetics don't work for me". While most cases probably reflect inadequate technique or drug and dose selection, or conditions of inflammation or hyperalgesia as described above, genetic variations in sodium channels could lead to reduced local anesthetic responsiveness in some patients (45,46). Sodium channel variants are implicated in a rapidly-expanding spectrum of neurologic(47-49) and cardiovascular(50,51) disorders.

4. Selected approaches to making a "better" local anesthetic Available local anesthetics have shortcomings. They are not sufficiently selective for sensory, autonomic, or motor blockade. True "differential epidural block" is not achievable by currently available agents. They have toxicities as noted above. In many contexts, the duration of analgesia is too short. Efforts to produce newer and/or better local anesthetics have followed several directions.

a. Use of single enantiomers, rather than racemic mixtures. Ropivacaine and levo-bupivacaine were developed based on the finding of degrees of stereoselectivity in cardiotoxicity and degrees of sensory versus motor blockade for these agents in preclinical studies. These agents produce modest improvement in either sensory selectivity or therapeutic indices (ratio of effective to toxic doses) compared to the racemic mixtures. The degree of improvement in sensory selectivity has appeared variable in previous studies(52). Ropivacaine may have up to a 1.5- 2-fold increase in therapeutic index compared with bupivacaine in both infant and adult rats(53). This difference may be relevant for infants, since the maximum safe infusion rate for epidural bupivacaine in neonates and younger infants, roughly 0.2 mg/kg/hr(54), is probably insufficient as the sole agent to provide epidural analgesia for a substantial fraction of neonates and younger infants, even with optimal dermatomal placement.

b. Sustained-release formulations Peripheral nerve blocks are useful, but they sometimes don't last long enough to influence the overall course of postoperative recovery. One approach to prolonged-duration local anesthesia is to deliver local anesthetics using a sustained-release system, such as liposomes(55,56), microspheres (57-59) , or other types of microparticles. Our group developed formulations using bupivacaine, small amounts of the anti-inflammatory steroid, dexamethasone, and a biodegradable polymer, PLGA, much like that in some types of absorbable suture material(57-59). Animal studies showed excellent safety, with low plasma bupivacaine concentrations, and nerve blockade lasting 2-7 days, depending on the species, dose, and site of administration. Initial human studies also showed excellent promise. Commercial development stalled in Phase 2 studies, but I remain optimistic that some type of formulation can be effective for prolonged infiltration anesthesia for surgery in the thorax and abdomen.

c. Old molecules previously used for other purposes. Two commonly used systemic drugs have been re-evaluated as local anesthetics: amitriptyline (60) (61) (a tricyclic antidepressant widely used orally for treatment of neuropathic pain), ketamine(62) (a well-known sedative-analgesic-anesthetic agent which acts as an antagonist at NMDA receptors and probably has several other sites of action). Recent animal studies suggest that both agents produce conduction blockade *in vivo*, and appear to block sodium channels *in vitro*. It remains to be determined whether these agents will afford clinically important improvements in duration, safety or sensory selectivity. Local neurotoxicity may limit the clinical safety of amitriptyline (63) .

d. Site 1 Sodium Channel Toxins Tetrodotoxin (TTX) and saxitoxin (STX) have long been known to bind to a specific site on sodium channels, designated as site 1, and to have extremely high potency in blocking some, but not all, sodium channels in isolated cell bodies or axons. They were rejected as clinically useful local anesthetics because in early studies there was severe systemic toxicity (diaphragm paralysis and vasodilation) at most doses sufficient to produce conduction blockade of peripheral nerves. Studies by Kohane et al. in our group using combinations of site 1 toxins with either vasoconstrictors or conventional local anesthetics suggest that these and other combinations may sufficiently improve therapeutic indices to permit use as long-acting local anesthetics(64,65).

e. Butamben Butamben is a formulation used to provide prolonged analgesia, especially for patients with terminal malignancy. There remains some controversy about its mechanisms of action, but it appears to have both aspects of a semi-controlled sustained release system, actions as a neurolytic agent (66), and actions on T-type calcium channels and subclasses of potassium channels (4) .

f. New molecules that target sodium channel subtypes. There are a large number of different sodium channel subtypes in different mammalian tissues. Several groups of investigators used molecular biologic approaches to identify sodium channels which are expressed predominantly in smaller sensory neurons(67). Some of these sodium channels, (denoted as either SNS, PN or NaN subtypes in different publications), are relatively resistant to blockade by TTX. Rodent models of inflammation and nerve injury have produce some variability in results; in some studies expression of certain SNS channels is increased by inflammation and decreased by painful nerve injury (67). There has been some drug development activity in targeting these sodium channel subtypes for development of analgesics, but available information in this regard is too preliminary to permit conclusions at present.

5. Conclusions

Local anesthetics are extremely useful, but their safety and effectiveness would be improved by development of agents that produce less systemic and local toxicity, by better ability to control duration and by agents that could produce more sensory-selective blockade.

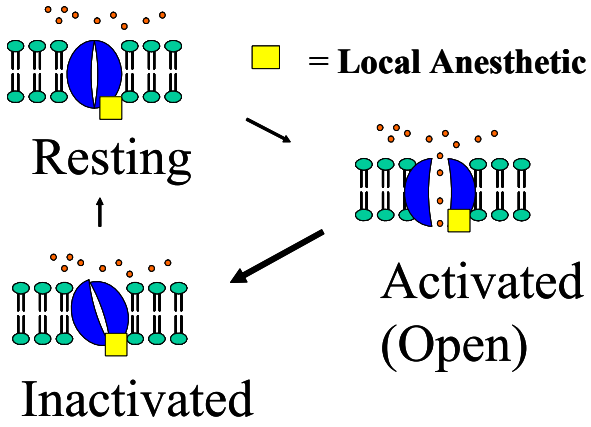
6. References

1. Strichartz G, Berde CB. Local Anesthetics. In: Miller RD, ed. Anesthesia. 6th ed. Philadelphia, PA: Elsevier, 2005:573-603.
2. Komai H, McDowell TS. Local anesthetic inhibition of voltage-activated potassium currents in rat dorsal root ganglion neurons. Anesthesiology 2001;94:1089-95.
3. Zhou W, Arrabit C, Choe S, Slesinger PA. Mechanism underlying bupivacaine inhibition of G protein-gated inwardly rectifying K+ channels. Proc. Nat Acad Sci. USA 2001;98:6482-7.
4. Beekwilder JP, O'Leary ME, van den Broek LP et al. Kv1.1 channels of dorsal root ganglion neurons are inhibited by n-butyl-p-aminobenzoate, a promising anesthetic for the treatment of chronic pain. Journal of Pharmacology & Experimental Therapeutics. 2003;304:531-8.
5. Sugimoto M, Uchida I, Mashimo T. Local anaesthetics have different mechanisms and sites of action at the recombinant N-methyl-D-aspartate (NMDA) receptors. British Journal of Pharmacology 2003;138:876-82.
6. Pawson L, Bolanowski SJ. Voltage-gated sodium channels are present on both the neural and capsular structures of Pacinian corpuscles. Somatosensory & Motor Research. 2002;19:231-7.
7. Beloeil H, Asehnoune K, Moine P et al. Bupivacaine's action on the carrageenan-induced inflammatory response in mice: cytokine production by leukocytes after ex-vivo stimulation. Anesthesia & Analgesia 2005;100:1081-6.
8. Hahnenkamp K, Theilmeier G, Van Aken HK, Hoenemann CW. The effects of local anesthetics on perioperative coagulation, inflammation, and microcirculation. Anesthesia & Analgesia 2002;94:1441-7.
9. Drasner K. Local anesthetic neurotoxicity: clinical injury and strategies that may minimize risk. Regional Anesthesia & Pain Medicine 2002;27:576-80.
10. Amaniti E, Drampa F, Kouzi-Koliakos K et al. Ropivacaine myotoxicity after single intramuscular injection in rats. European Journal of Anaesthesiology 2006;23:130-5.
11. Beloeil H, Ababneh Z, Chung R et al. Effects of bupivacaine and tetrodotoxin on carrageenan-induced hindpaw inflammation in rats. I. Hyperalgesia, Edema, and Systemic Cytokines. Anesthesiology 2006, in press.
12. Beloeil H, Ji R-R, Berde CB. Effects of bupivacaine and tetrodotoxin on carrageenan-induced hindpaw inflammation in rats: II. cytokines and p38 mitogen-activated protein kinases in dorsal root ganglia and spinal cord. Anesthesiology 2006, in press.
13. Popitz-Bergez FA, Leeson S, Strichartz GR, Thalhammer JG. Relation between functional deficit and intraneural local anesthetic during peripheral nerve block. A study in the rat sciatic nerve. Anesthesiology 1995;83:583-92.
14. Masuda T, Cairns BE, Sadhasivam S et al. Epinephrine prevents muscle blood flow increases after perineural injection of tetrodotoxin. Anesthesiology 2004;101:1428-34.
15. Kehlet H, Mogensen T. Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme. British Journal of Surgery 1999;86:227-30.
16. Barratt SM, Smith RC, Kee AJ et al. Multimodal analgesia and intravenous nutrition preserves total body protein following major upper gastrointestinal surgery. Regional Anesthesia & Pain Medicine 2002;27:15-22.

17. Chaplan SR, Bach FW, Shafer SL, Yaksh TL. Prolonged alleviation of tactile allodynia by intravenous lidocaine in neuropathic rats. Anesthesiology 1995;83:775-85.
18. Sinnott CJ, Garfield JM, Strichartz GR. Differential efficacy of intravenous lidocaine in alleviating ipsilateral versus contralateral neuropathic pain in the rat. Pain 1999;80:521-31.
19. Devor M, Wall PD, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. Pain 1992;48:261-8.
20. Nagy I, Woolf CJ. Lignocaine selectively reduces C fibre-evoked neuronal activity in rat spinal cord in vitro by decreasing N-methyl-D-aspartate and neurokinin receptor-mediated post-synaptic depolarizations; implications for the development of novel centrally acting analgesics. Pain 1996;64:59-70.
21. Koppert W, Weigand M, Neumann F et al. Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. Anesthesia & Analgesia 2004;98:1050-5.
22. Thomas J, Kronenberg R, Cox MC et al. Intravenous lidocaine relieves severe pain: results of an inpatient hospice chart review. Journal of Palliative Medicine 2004;7:660-7.
23. Xie W, Strong J, Meij J et al. Neuropathic pain: early spontaneous afferent activity is the trigger. Pain 2005;116:243-56.
24. Moore DC, Bridenbaugh LD, Thompson GE et al. Bupivacaine: a review of 11,080 cases. Anesthesia & Analgesia 1978;57:42-53.
25. Giaufre E, Dalens B, Gombert A. Epidemiology and morbidity of regional anesthesia in children: a one-year prospective survey of the French-Language Society of Pediatric Anesthesiologists. Anesthesia & Analgesia 1996;83:904-12.
26. Flandin-Blety C, Barrier G. Accidents following extradural analgesia in children. The results of a retrospective study. Paediatric Anaesthesia 1995;5:41-6.
27. Morray JP, Geiduschek JM, Ramamoorthy C et al. Anesthesia-related cardiac arrest in children: initial findings of the Pediatric Perioperative Cardiac Arrest (POCA) Registry. Anesthesiology 2000;93:6-14.
28. Irita K, Kawashima Y, Morita K et al. [Critical incidents during regional anesthesia in Japanese Society of Anesthesiologists-Certified Training Hospitals: an analysis of responses to the annual survey conducted between 1999 and 2002 by the Japanese Society of Anesthesiologists]. Masui Japanese Journal of Anesthesiology 2005;54:440-9.
29. Grazer FM, de Jong RH. Fatal outcomes from liposuction: census survey of cosmetic surgeons. Plastic & Reconstructive Surgery 2000;105:436-46.
30. Berde C. Local anesthetics in infants and children: an update. Paediatric Anaesthesia 2004;14:387-93.
31. Henderson K, Sethna NF, Berde CB. Continuous caudal anesthesia for inguinal hernia repair in former preterm infants. Journal of Clinical Anesthesia 1993;5:129-33.
32. Tobias JD, Rasmussen GE, Holcomb GW, 3rd et al. Continuous caudal anaesthesia with chloroprocaine as an adjunct to general anaesthesia in neonates. Canadian Journal of Anaesthesia 1996;43:69-72.
33. FDA. Public Health Advisory on Benzocaine Sprays. February, 2006: http://www.fda.gov/cder/drug/advisory/benzocaine.htm.
34. Bainton CR, Strichartz GR. Concentration dependence of lidocaine-induced irreversible conduction loss in frog nerve. Anesthesiology 1994;81:657-67.
35. Cairns BE, Gambarota G, Dunning PS et al. Activation of peripheral excitatory amino acid receptors decreases the duration of local anesthesia. Anesthesiology 2003;98:521-9.
36. Cairns BE, Svensson P, Wang K et al. Activation of peripheral NMDA receptors contributes to human pain and rat afferent discharges evoked by injection of glutamate into the masseter muscle. Journal of Neurophysiology 2003;90:2098-105.
37. Choi RH, Birknes JK, Popitz-Bergez FA et al. Pharmacokinetic nature of tachyphylaxis to lidocaine: peripheral nerve blocks and infiltration anesthesia in rats. Life Sci 1997;61:177-84.
38. Lee KC, Wilder RT, Smith RL, Berde CB. Thermal hyperalgesia accelerates and MK-801 prevents the development of tachyphylaxis to rat sciatic nerve blockade. Anesthesiology 1994;81:1284-93.
39. Wilder RT, Sholas MG, Berde CB. NG-nitro-L-arginine methyl ester (L-NAME) prevents tachyphylaxis to local anesthetics in a dose-dependent manner. Anesthesia & Analgesia 1996;83:1251-5.
40. Wang C, Sholas MG, Berde CB et al. Evidence that spinal segmental nitric oxide mediates tachyphylaxis to peripheral local anesthetic nerve block. Acta Anaesthesiologica Scandinavica 2001;45:945-53.
41. Mogensen T, Simonsen L, Scott NB et al. Tachyphylaxis associated with repeated epidural injections of lidocaine is not related to changes in distribution or the rate of elimination from the epidural space. Anesth Analg 1989;69:180-4.

42. Mogensen T, Scott NB, Lund C et al. The roles of acute and chronic pain in regression of sensory analgesia during continuous epidural bupivacaine infusion. Anesth Analg 1988;67:737-40.
43. Lund C, Mogensen T, Hjortso NC, Kehlet H. Systemic morphine enhances spread of sensory analgesia during postoperative epidural bupivacaine infusion. Lancet 1985;2(8465):1156-7.
44. Mercadante S, Villari P, Ferrera P, Arcuri E. Local anesthetic switching for intrathecal tachyphylaxis in cancer patients with pain. Anesthesia & Analgesia 2003;97:187-9.
45. Arendt-Nielsen L, Kaalund S, Bjerring P, Hogsaa B. Insufficient effect of local analgesics in Ehlers Danlos type III patients (connective tissue disorder). Acta Anaesthesiologica Scandinavica 1990;34:358-61.
46. Arendt-Nielsen L, Kaalund S, Hogsaa B et al. The response to local anaesthetics (EMLA-cream) as a clinical test to diagnose between hypermobility and Ehlers Danlos type III syndrome. Scandinavian Journal of Rheumatology 1991;20:190-5.
47. Craner MJ, Damarjian TG, Liu S et al. Sodium channels contribute to microglia/macrophage activation and function in EAE and MS. Glia 2005;49:220-9.
48. Cummins TR, Dib-Hajj SD, Waxman SG. Electrophysiological properties of mutant Nav1.7 sodium channels in a painful inherited neuropathy. Journal of Neuroscience 2004;24:8232-6.
49. Waxman SG. Cerebellar dysfunction in multiple sclerosis: evidence for an acquired channelopathy. Progress in Brain Research 2005;148:353-65.
50. Ackerman MJ, Splawski I, Makielski JC et al. Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: Implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing. Heart Rhythm 2004;1:600-7.
51. Brugada P, Brugada R, Antzelevitch C, Brugada J. The Brugada Syndrome. Archives des Maladies du Coeur et des Vaisseaux 2005;98:115-22.
52. Polley LS, Columb MO, Naughton NN et al. Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor: implications for therapeutic indexes. Anesthesiology 1999;90:944-50.
53. Kohane DS, Sankar WN, Shubina M et al. Sciatic nerve blockade in infant, adolescent, and adult rats: a comparison of ropivacaine with bupivacaine. Anesthesiology 1998;89:1199-208.
54. Larsson BA, Lonnqvist PA, Olsson GL. Plasma concentrations of bupivacaine in neonates after continuous epidural infusion. Anesthesia & Analgesia 1997;84:501-5.
55. Grant GJ, Vermeulen K, Langerman L et al. Prolonged analgesia with liposomal bupivacaine in a mouse model. Regional Anesthesia 1994;19:264-9.
56. Boogaerts J, Lafont N, Carlino S et al. Biodistribution of liposome-associated bupivacaine after extradural administration to rabbits. British Journal of Anaesthesia 1995;75:319-25.
57. Castillo J, Curley J, Hotz J et al. Glucocorticoids prolong rat sciatic nerve blockade in vivo from bupivacaine microspheres. Anesthesiology 1996;85:1157-66.
58. Curley J, Castillo J, Hotz J et al. Prolonged regional nerve blockade. Injectable biodegradable bupivacaine/polyester microspheres. Anesthesiology 1996;84:1401-10.
59. Drager C, Benziger D, Gao F, Berde CB. Prolonged intercostal nerve blockade in sheep using controlled-release of bupivacaine and dexamethasone from polymer microspheres. Anesthesiology 1998;89:969-79.
60. Gerner P, Mujtaba M, Sinnott CJ, Wang GK. Amitriptyline versus bupivacaine in rat sciatic nerve blockade. Anesthesiology 2001;94:661-7.
61. Khan MA, Gerner P, Kuo Wang G. Amitriptyline for prolonged cutaneous analgesia in the rat. Anesthesiology 2002;96:109-16.
62. Wagner LE, 2nd, Gingrich KJ, Kulli JC, Yang J. Ketamine blockade of voltage-gated sodium channels: evidence for a shared receptor site with local anesthetics. Anesthesiology 2001;95:1406-13.
63. Estebe J-P, Myers RR. Amitriptyline Neurotoxicity. Anesthesiology 2004;100:1519-25.
64. Kohane DS, Yieh J, Lu NT et al. A re-examination of tetrodotoxin for prolonged duration local anesthesia. Anesthesiology 1998;89:119-31.
65. Kohane DS, Lu NT, Gokgol-Kline AC et al. The local anesthetic properties and toxicity of saxitonin homologues for rat sciatic nerve block in vivo. Regional Anesthesia & Pain Medicine 2000;25:52-9.
66. Shulman M, Harris JE, Lubenow TR et al. Comparison of epidural butamben to celiac plexus neurolytic block for the treatment of the pain of pancreatic cancer. Clinical Journal of Pain 2000;16:304-9.
67. Cummins TR, Waxman SG. Downregulation of tetrodotoxin-resistant sodium currents and upregulation of a rapidly repriming tetrodotoxin-sensitive sodium current in small spinal sensory neurons after nerve injury. Journal of Neuroscience 1997;17:3503-14.

Figure 1 **Modulated Receptor Hypothesis**



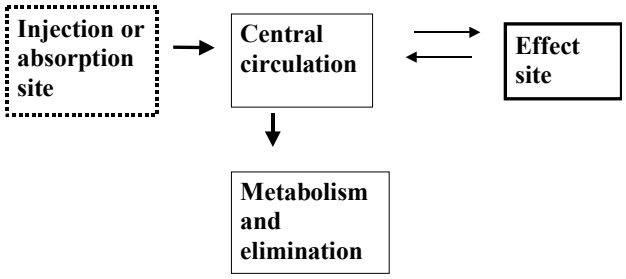
Simplified model of differential binding of local anesthetics to sodium channels in different conformations. Local anesthetics binding changes the relative stability of different conformations and alters the kinetics of channel opening and inactivation.

Most Drugs

Figure 2

a.

Systemically-active drugs have a series relationship between the site of administration, the central circulation, and the effect site.



Local Anesthetics

b.

Local anesthetics have a parallel relationship between the site of administration, the central circulation, and the effect site.