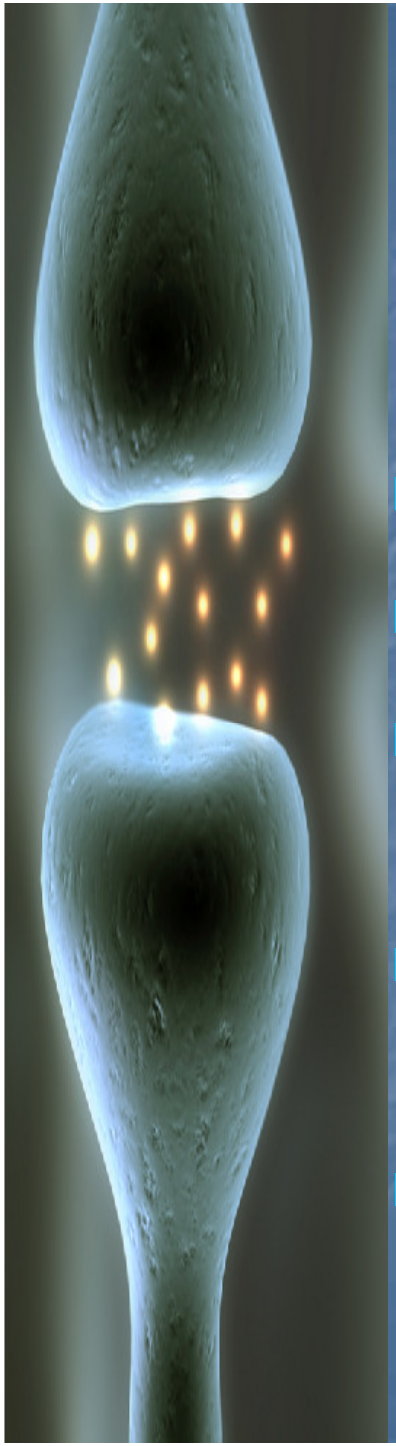
NMDA Receptor Antagonists:
Preventing windup pain

Presented by Lee Ellingson, MHS CRNA
Staff CRNA, Sanford Health-Meritcare

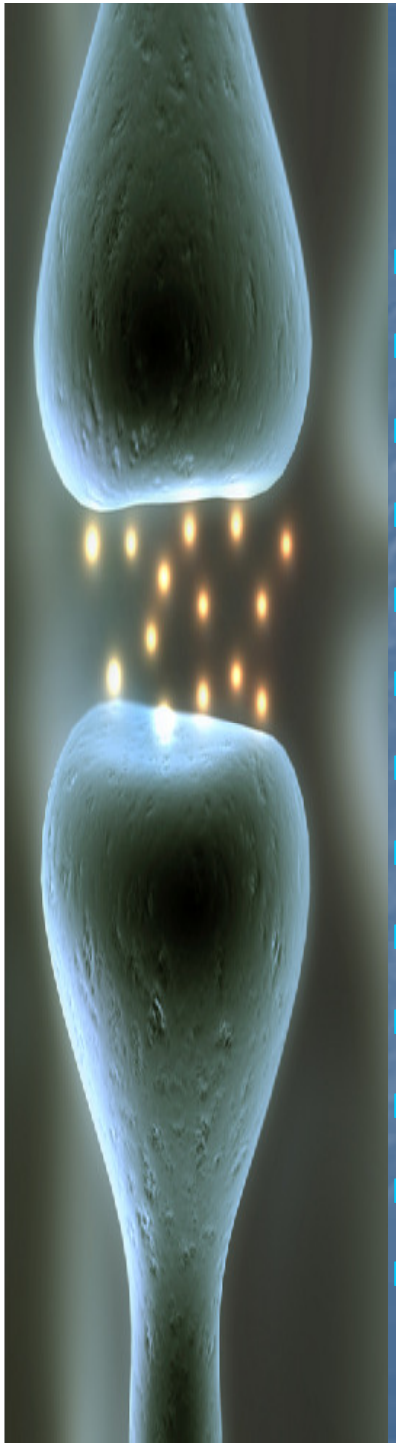
Objectives

- Review basic anatomy and physiology of pain responses.
- Analyze pathophysiological / chronic pain responses as related to NMDA receptor activation.
- Examine the longterm ramifications of NMDA receptor induction.
- Compare and contrast perioperative pharmacologic methods of antagonizing NMDA receptors: past, present and future.



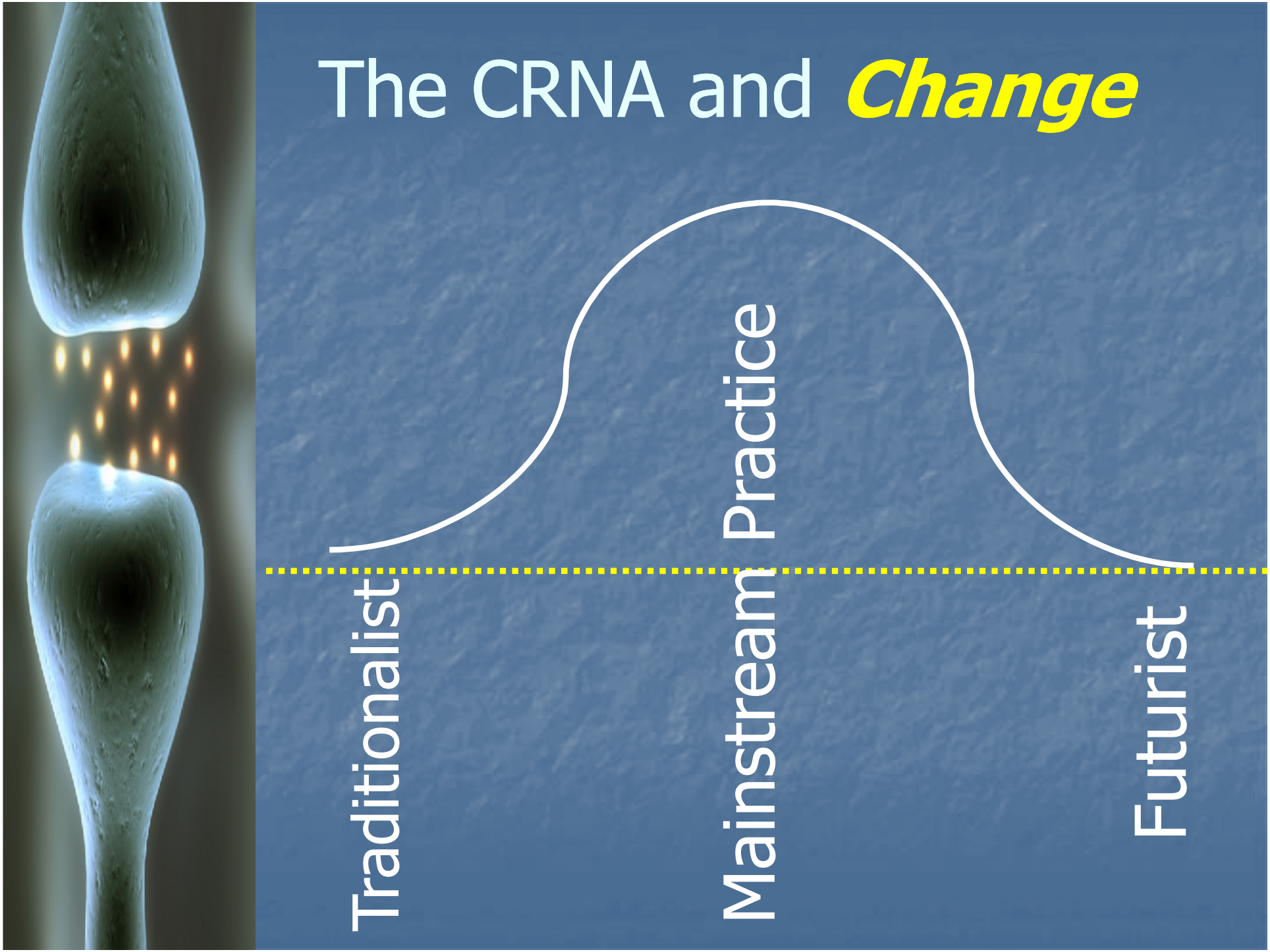
Anesthesia-definition/goals

- Reversible Amnesia
- Reversible Loss of Responsiveness
- Reversible Loss of Skeletal Muscle Reflex
- Reversible Obtunding of Autonomic Reflexes
- ???*Reversible*??? Analgesia



Brief history of anesthesia

- 1840s: Nitrous Oxide, Ether, Chloroform
- 1884: Cocaine in eye surgery
- 1898: Spinal anesthesia used in surgery
- 1930s: Intravenous anesthesia w/ barbiturates
- 1943: Lidocaine synthesized
- 1954: Halothane first used
- 1970s: Fentanyl and analogs
- 1980s: Epidural/Spinal narcotics
- 1990s: Ketorolac and Cox2 inhibitors
- 1990s: Preemptive use of local anesthesia
- 1995: NMDA receptor antagonism
- 2005: Dexmedetomidine
- 2010----------→ Even more change


The CRNA and Change
Traditionalist
Mainstream Practice
Futurist

Approaching recommendations for change (*or non-change*) with caution

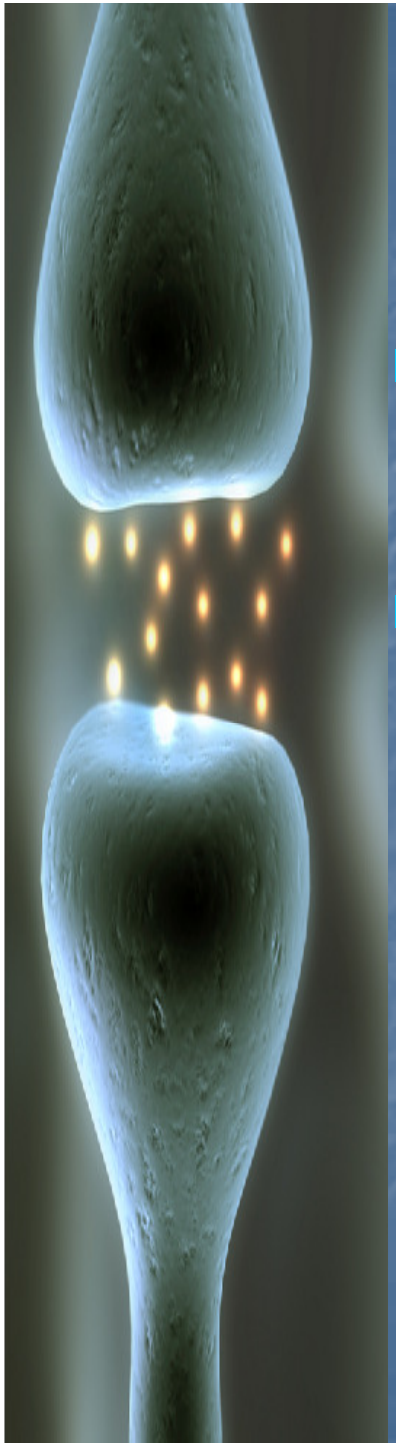
Fill in the blank

The lack of analgesic action of _____ is an undesirable property of this drug and limits its safe use as sole anaesthetic.

The answer is

Halothane

Dundee J, Moore J. Alterations in response to somatic pain associated with anesthesia. IV: the effect of sub-anaesthetic concentrations of inhalation agents. Br J Anaesth 1960;32:453–9

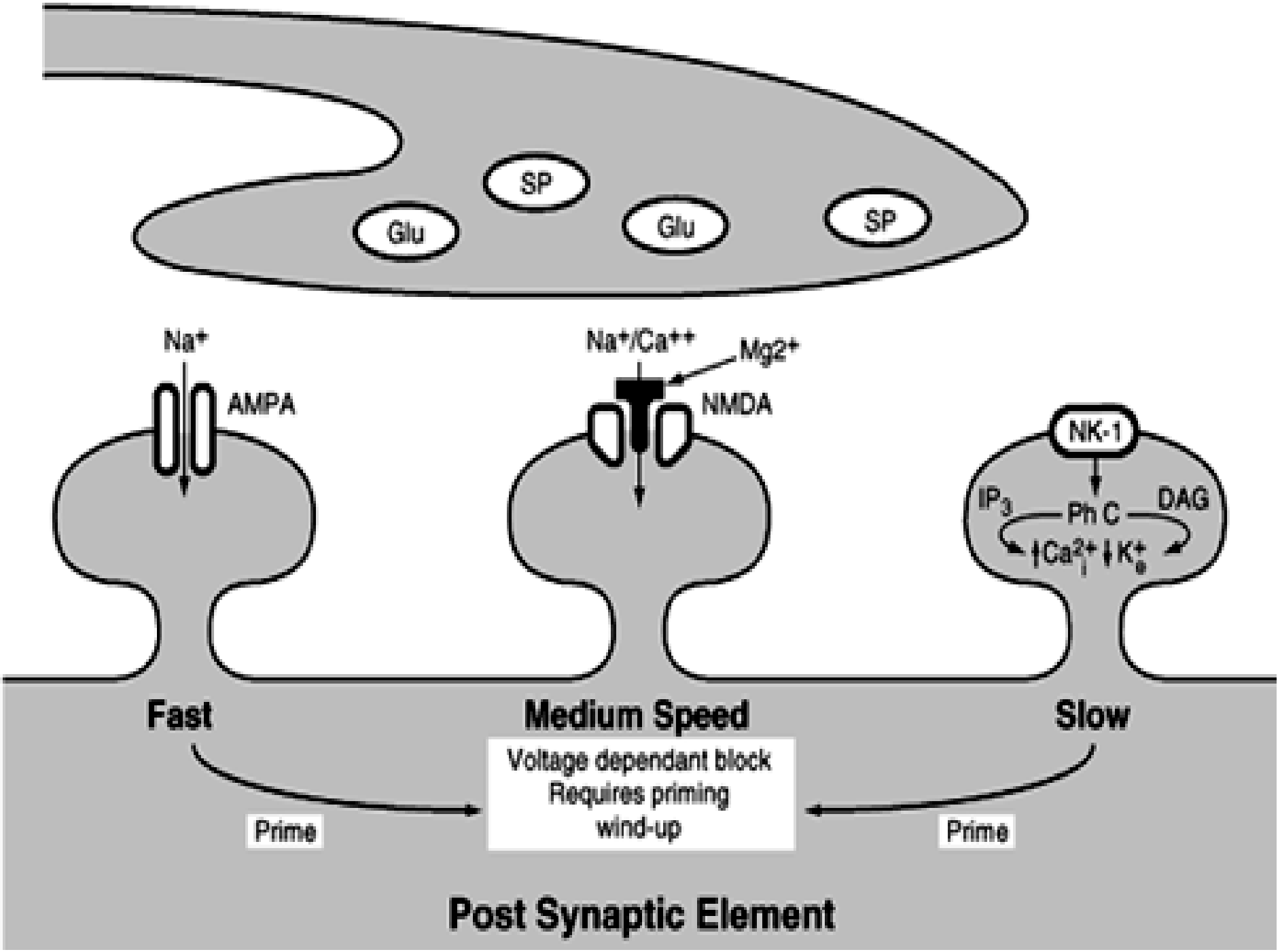


NMDA Anatomy/Physiology

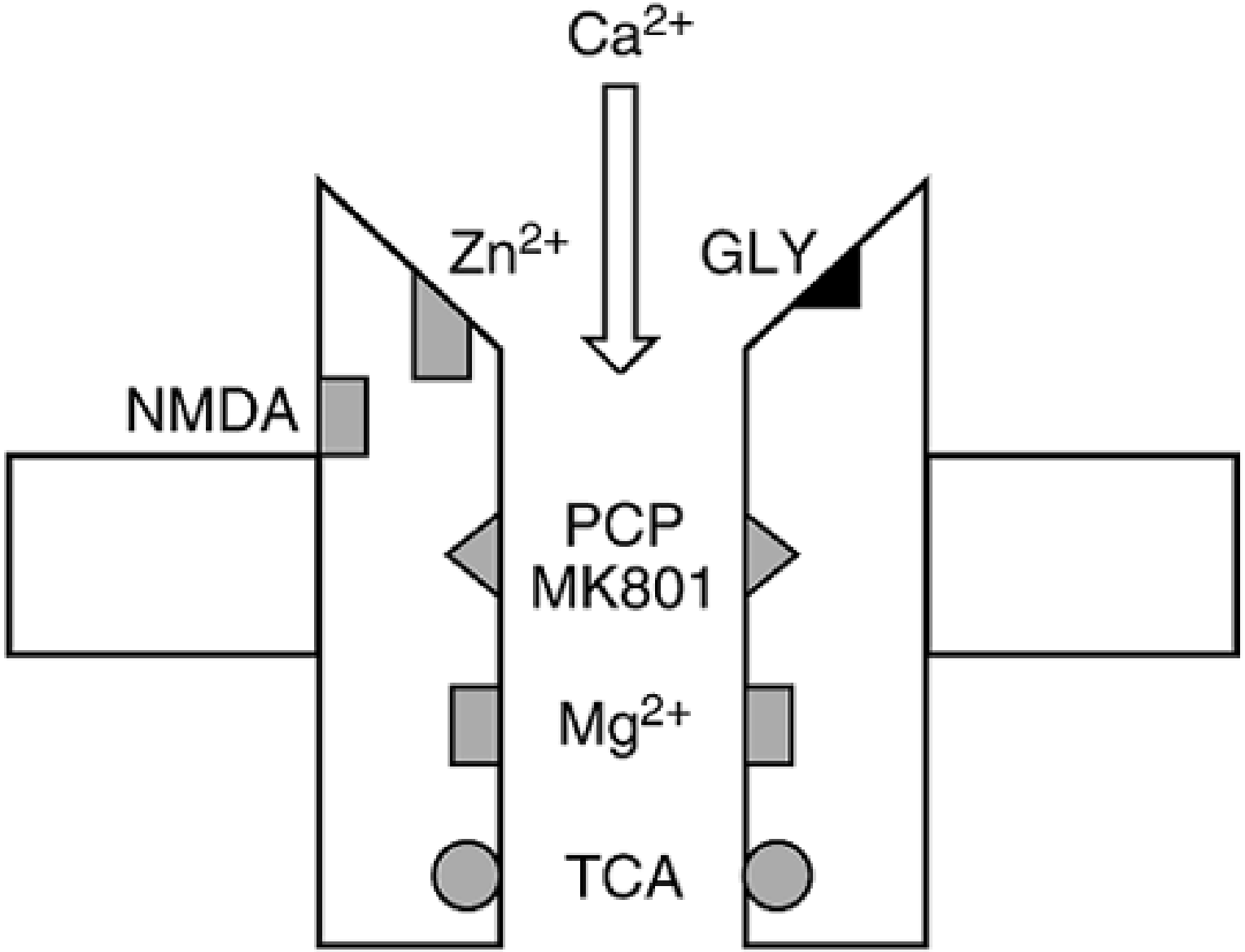
- NMDA (*N*-methyl *D*-aspartate)
- Ionotropic Glutamate receptor
  - Nonselective to cations (Na^{+}, Ca^{++}, K^{+})
  - Ligand operated (glutamate & glycine)
  - Voltage dependent (blocked by Mg^{++})

NMDA Anatomy/Physiology

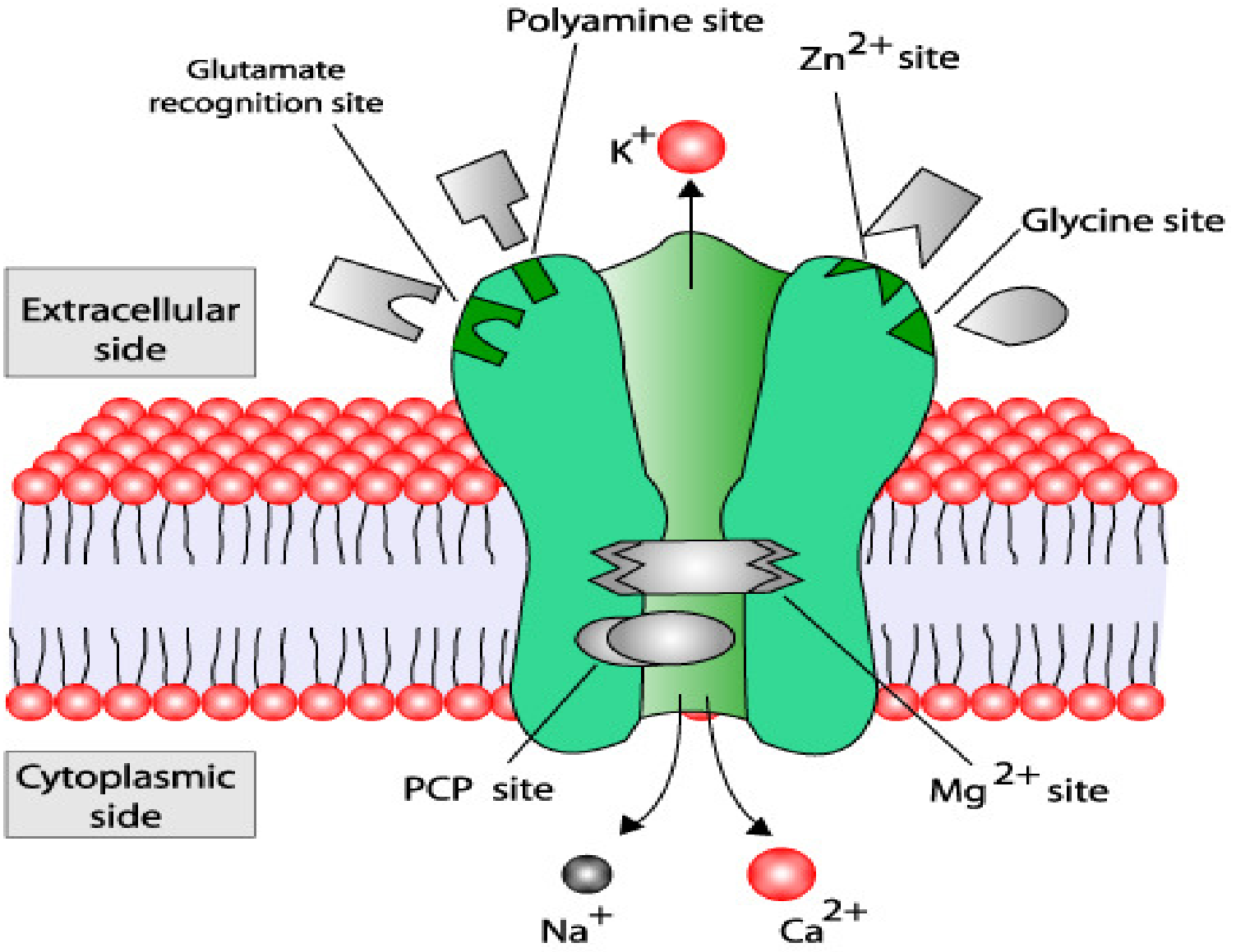
- NMDA receptor activation
  - By co-ligands: glycine and glutamate
  - Subunits (AMPA and Neurokinin1) cause exit of blocking ion, $Mg^{++,}$ from NMDA ion channel.
  - Na^{+} & Ca^{++} enter while K^{+} exits; thus, producing membrane depolarization


SP
Glu
Glu
SP
Na+
AMPA
Na+/Ca++
Mg2+
NMDA
NK-1
IP3
Ph C
DAG
↑Ca2+i ↓K+e
Fast
Medium Speed
Slow
Voltage dependant block
Requires priming
wind-up
Prime
Prime
Post Synaptic Element

NMDA Anatomy/Physiology



NMDA Anatomy/Physiology



NMDA Anatomy/Physiology

- NMDA receptors responsible for:
  - Neural plasticity
  - Learning and memory

NMDA Pathophysiology

- Excessive activation implicated in
  - Depressive/mood disorders
  - Schizophrenia
  - Alzheimers
  - Addiction
  - Oncogene induction
  - Chronic Pain

NMDA: Pathophysiology & Pain

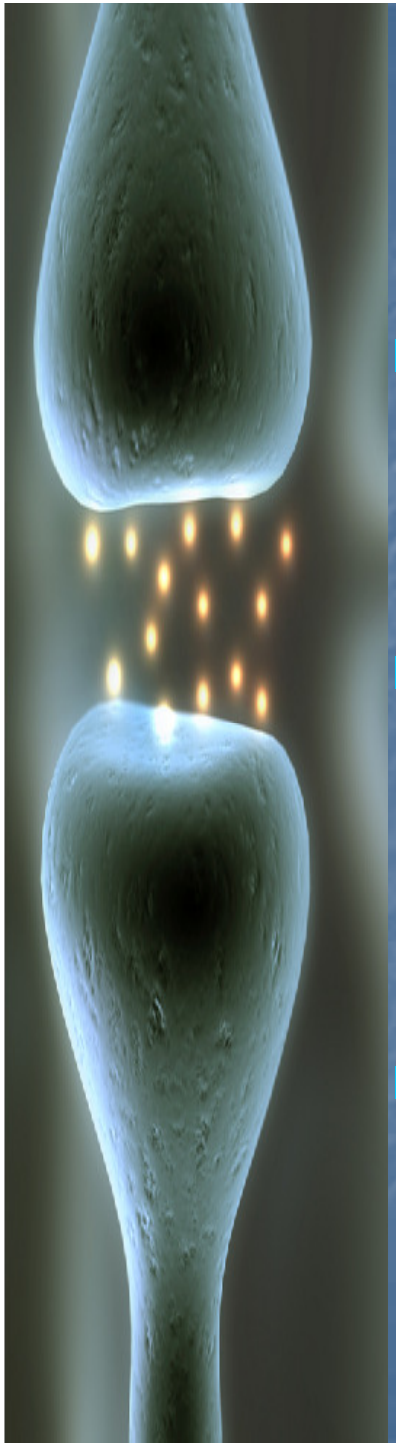
- Repeated or constant noxious input primes the NMDA receptor for chronic pain states (central sensitization)
  - Windup pain
  - Opioid tolerance
  - Opioid induced hyperalgesia
  - Receptive field size increase
  - Pain threshhold reduction
  - Longterm potentiation

Windup Pain

- Repeated noxious stimulus through C-fibers stimulates NMDA receptors in dorsal horn neurons in a progressively increasing manner.
  - Also termed Temporal Summation of Second Pain "TSSP"
  - Neural activity increases in a spontaneous "self-sustaining" manner
  - Hyper-excitability results
  - Central sensitization occurs at spinal and supraspinal levels

Opioid Tolerance

- Desensitization of Pronociceptive mechanisms.
- Patient requires escalating doses and more potent opioids
- Coadministration of NMDA antagonists prevents buildup of Morphine tolerance
- Coadministration of NMDA antagonists also prevents opioid withdrawal when decreasing doses.

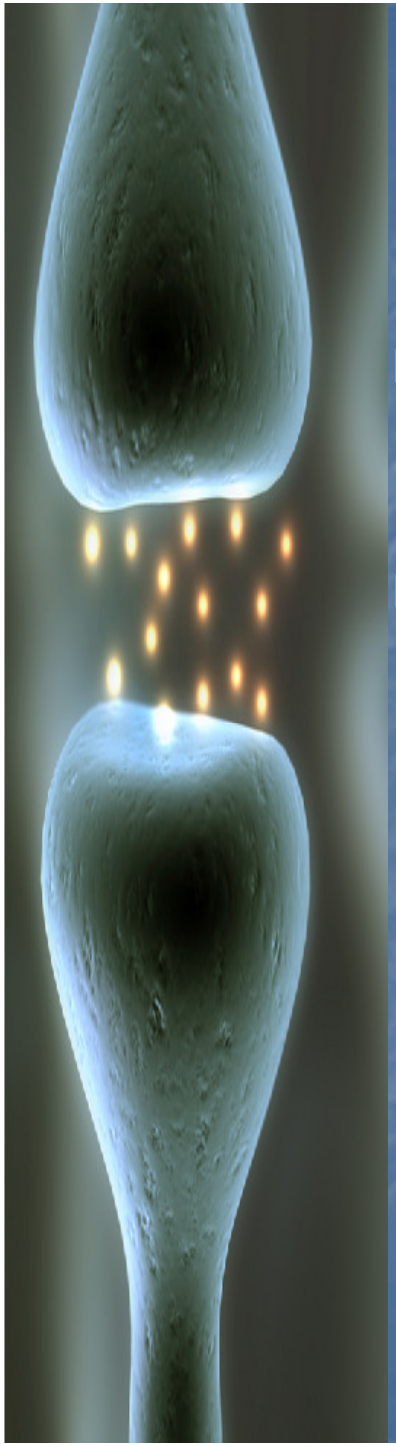


Opioid Induced Hyperalgesia

- Sensitization of pronociceptive mechanisms
- Long term use of opioids may Paradoxically cause increased pain sensitivity (hyperalgesia or allodynia)
- Escalating doses of opioids may actually further increase sensation of pain

Receptive field size expansion

- Spinal neurons activate a pain response to field normally outside site of injury.



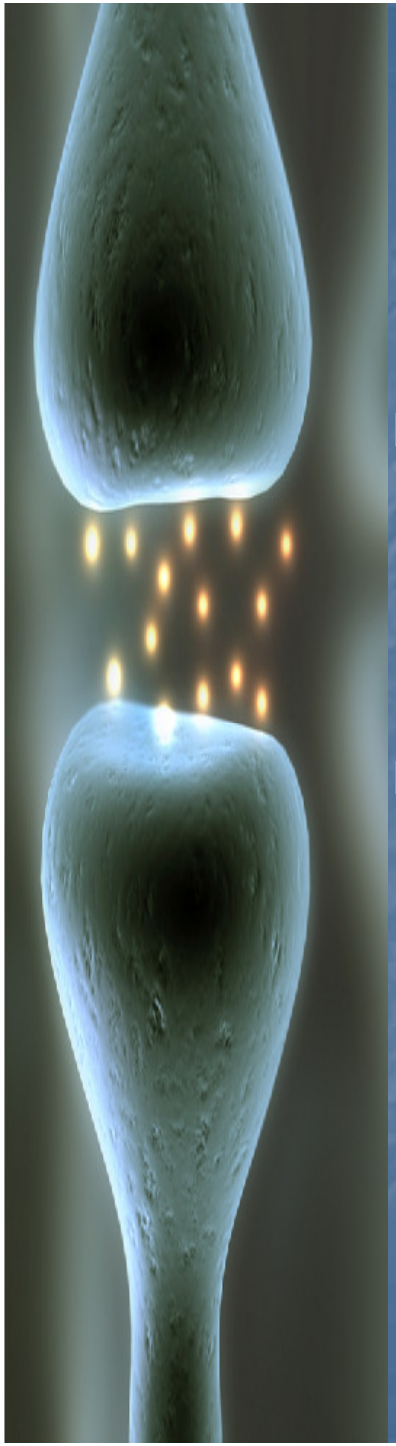
Pain threshold alteration

- Increase in magnitude and duration of neural responses.
- Decrease in threshold so that even non-nociceptive stimulation may be painful (eg. Allodynia)

Windup and Chronic Pain

- Windup and Central Sensitization can lead to biochemical cascades:
  - Phosphorylation of NMDA receptors and ion channels →
  - Transcription/Translation of genes →
  - Changing phenotype of neurons →
  - Increased excitability/sensitization
- This phenomenon reflects the neural plasticity of Long Term Potentiation.

Staud, R. et al. Maintenance of windup of second pain requires less frequent stimulation in fibromyalgia patients compared to normal controls. Pain 110 (2004) 689–696

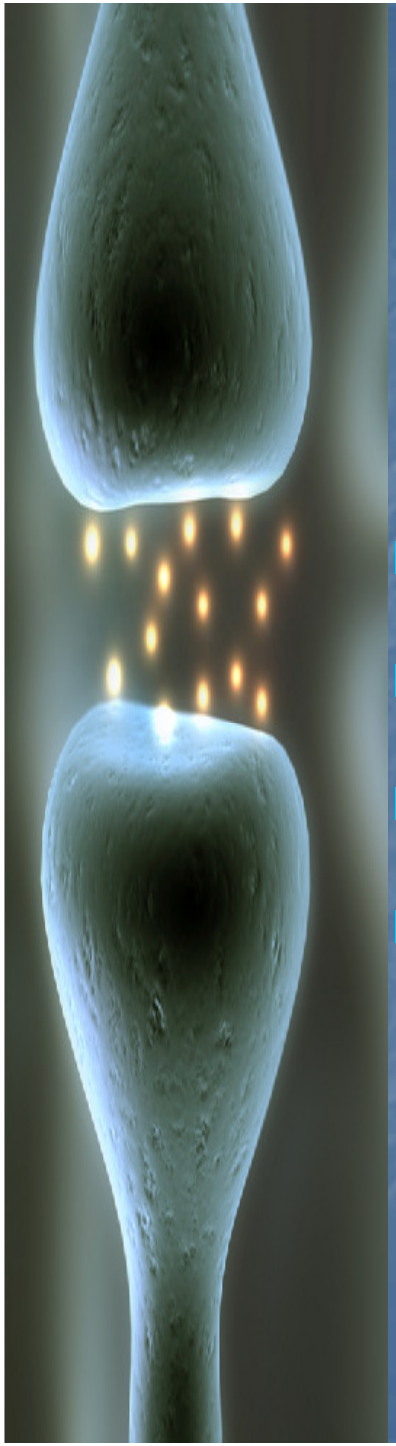


Significance of Chronic Pain Syndromes

- Untreated acute postop pain can evolve into chronic pain syndromes
- 80% of patients experience postop pain with 86% of these reporting moderate to extreme pain.

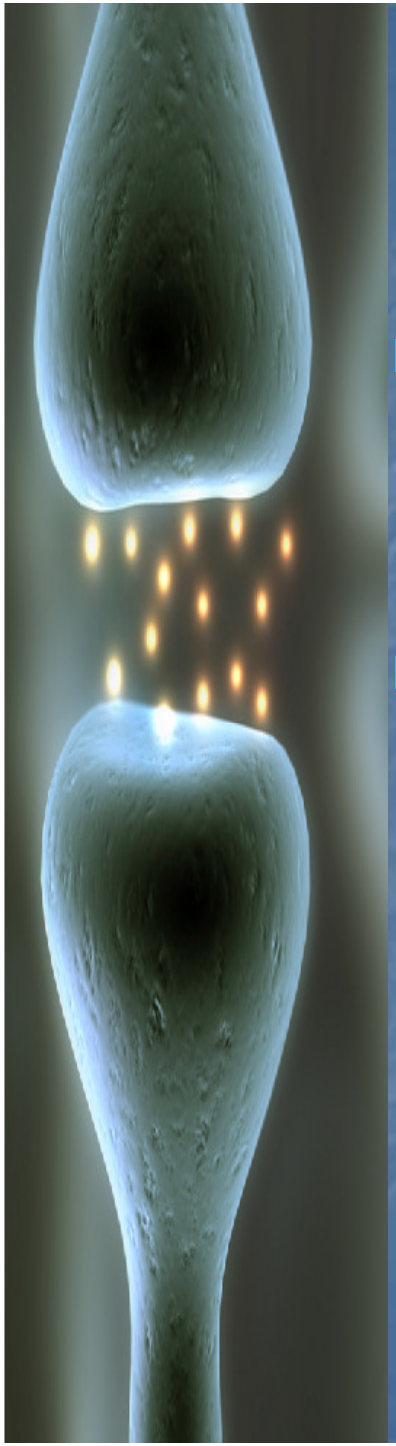
Are we doing our job?

Gottschalk,A. Severing the Link between Acute and Chronic Pain: The Anesthesiologist's Role in Preventive Medicine. Anesthesiology: November 2004; 101: 1063-1065



Incidence of Chronic Pain one year after surgery

- 70% after amputation
- 50% after thoracotomy
- 50% after mastectomy
- 25% after sternotomy



Chronic Pain Predictors

- Difficult to predict which patient will develop a chronic pain syndrome

However

- Early postoperative pain is the only significant predictor of persistent pain.

Katz, J. et al. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clinical Journal of Pain. 1996:12;50-55

Pain, Anxiety, *and Revenue*

- Fear of experiencing pain is most common concern of surgical preop patients– 59%
- 8% of these patients postpone surgery because of fear of pain.

Apfelbaum, J et al. Postoperative Pain Experience: Results from a National Survey Suggest Postoperative Pain Continues to Be Undermanaged. Anesthesia and Analgesia. 2003;97;534-540

The Bottom Line

- Chronic pain is associated with physiological and psychological consequences.
  - Mood swings
  - Depression
  - Sleep disturbances
  - Oncogenesis

- Chronic pain may indefinitely develop into a disease of itself

So where do we go from here?

An ounce of prevention…

- Preventive analgesia (Wall, 1988)
  - Early opioids
  - NSAIDS / COX2 Inhibitors
  - Local anesthetic- before incision
  - Regional anesthesia
  - NMDA antagonists
    - Magnesium
    - Ketamine
    - Dextromethorphan
    - Methadone
    - Adjuncts:Memantine (Namenda), Tricyclic antidepressants, Nicotine agonists

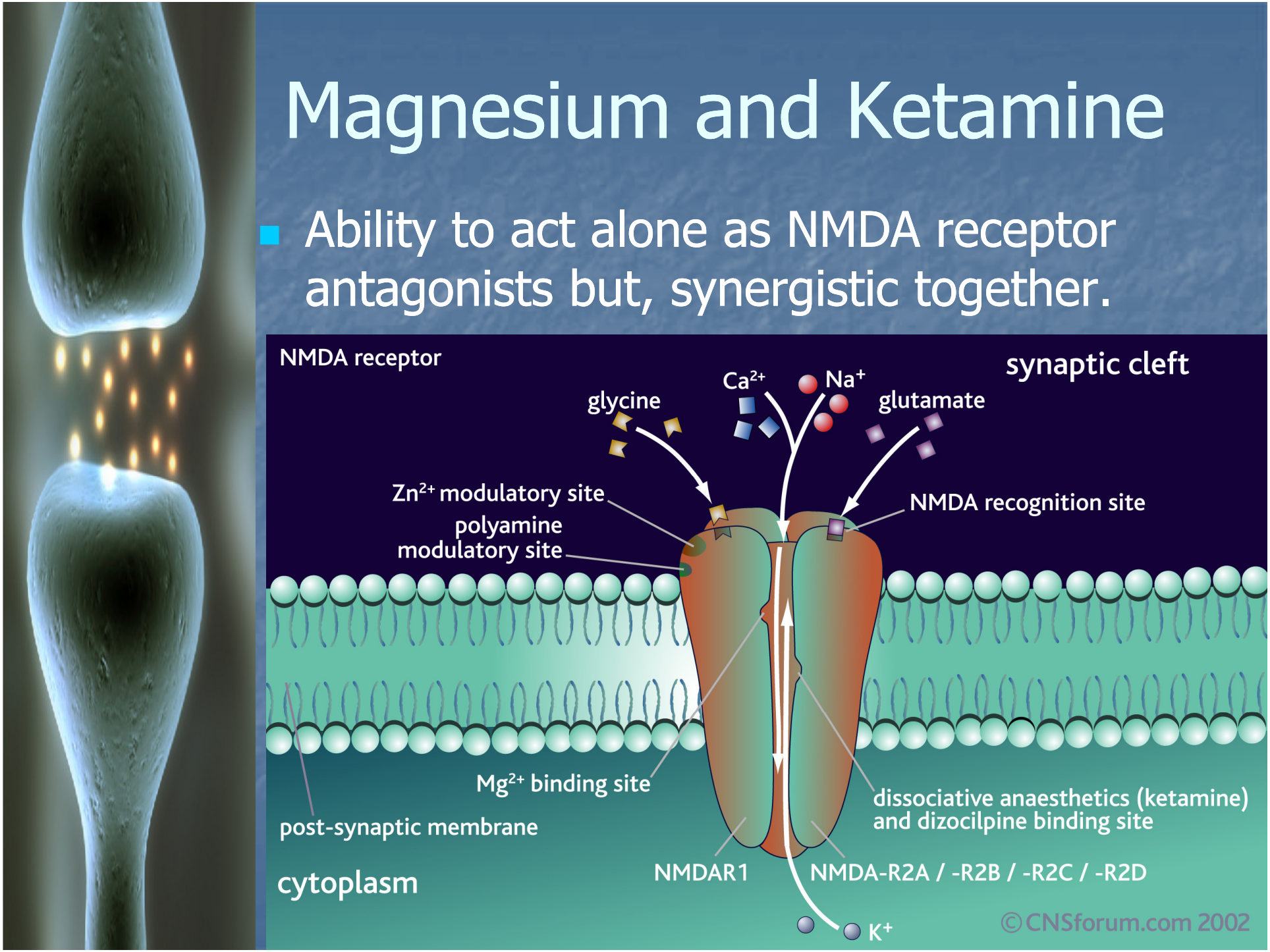
Magnesium and Ketamine

With these two super heroes…

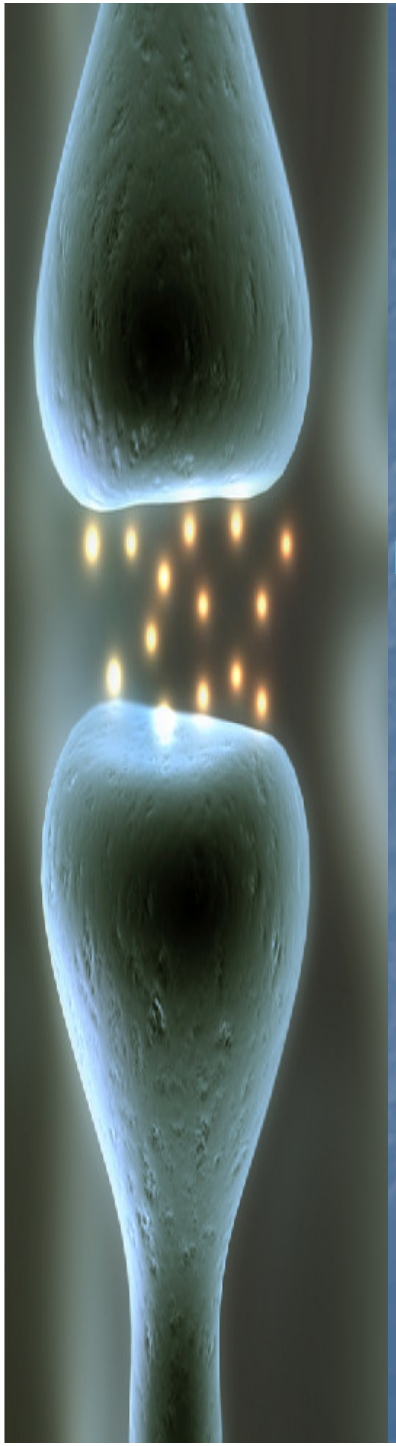
Wind up is Washed up !!

Magnesium and Ketamine

- Ability to act alone as NMDA receptor antagonists but, synergistic together.




Magnesium
The “drug” that don’t get no respect…



Magnesium Deficiency

- Magnesium deficiency is endemic in:
  - 7-11% of hospitalized patients
  - 40% of patients with concurrent electrolyte abnormalities

Fawcett, WJ et al. Magnesium: physiology and pharmacology. British Journal of Anaesthesia 1999: 83:2. pp 302-20

Magnesium levels in surgery

- Abdominal surgery is associated with hypomagnesemia
  - 5 studies revealed postop decreases in control group of 10-30% in serum Mg^{++}
  - 6 of 7 trials of bolus pretreatments of IV Mg^{++} yielded serum increases of 31-84%
- ?? Do lower serum levels of Mg^{++} affect pain levels postop.

Lysakowski, C. et al. Magnesium as an Adjuvant to Postoperative Analgesia: A Systematic Review of Randomized Trials. Anesthesia & Analgesia. 2007: 104,6; 1532-1539

Magnesium & analgesia

- Magnesium supplementation alone *may* decrease postop pain.
  - 8 trials (57% of all reviewed) reported significant decrease in postop analgesic use after intraop infusions of Mg^{++} .
    - Morphine use decreased 12-47% (1-2 days)
    - Fentanyl decreased 53-80% (2-4 hrs)

Lysakowski, C. et al. Magnesium as an Adjuvant to Postoperative Analgesia: A Systematic Review of Randomized Trials. Anesthesia & Analgesia. 2007: 104,6; 1532-1539

Magnesium-How to

- Initial Bolus of 30-50 mg/kg. (2 - 3.5 grams in 70kg patient)
- Infusion in surgery of 8-10 mg/kg/hr. (600 – 700 mg/hr).

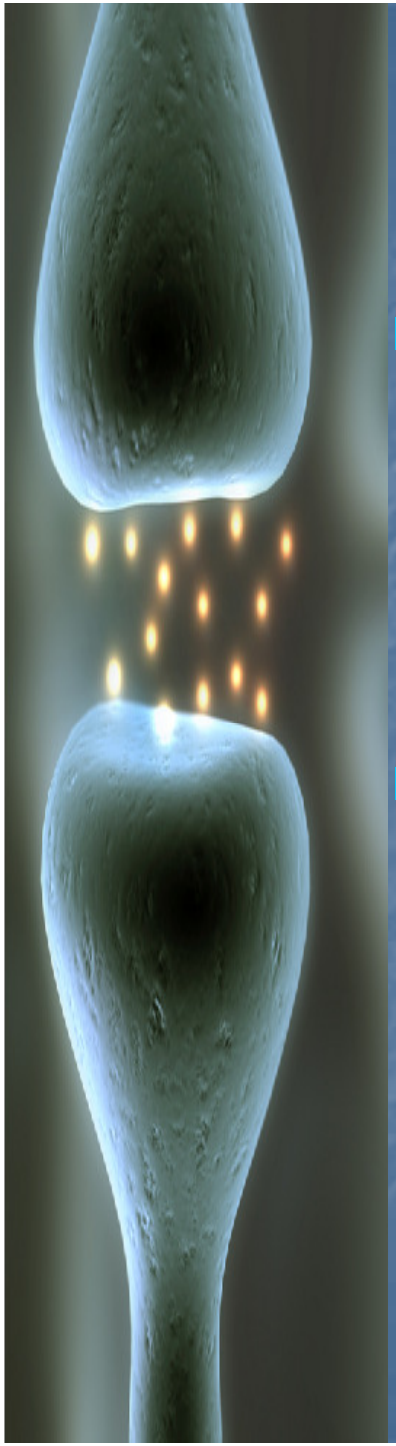
Koinig,H et al. Magnesium Sulfate Reduces Intra- and Postoperative Analgesic Requirements. Anesthesia & Analgesia. 1998: 87; 206-210

Telci,L et al. Evaluation of Magnesium Sulfate in reducing intraoperative anaesthetic requirements. British Journal of Anaesthesia. 2002: 89; 594-598

Magnesium: Clinical tidbits

- Even if only improves analgesia 57% of studies reveal there are other benefits.
  - Decreased Postop shivering
  - Improved postop sleep quality
  - Decreased airway irritability
  - Prevents succinylcholine myalgias
  - Decreased sympathetic responses
  - Improved skeletal muscle relaxation
  - Bronchodilitation

Fuchs-Buder,T. et al. Interaction of magnesium sulphate with vecuronium-induced neuromuscular block. British Journal of Anaesthesia. 1995;74:405-409



CAUTION

- Reduce Non depolarizer NMB drug induction and maintenance doses 25% when Mg^{++} is bolused 40mg/kg.
- Mg^{++} WILL recurarize patients if loading dose is given at end of anesthetic.

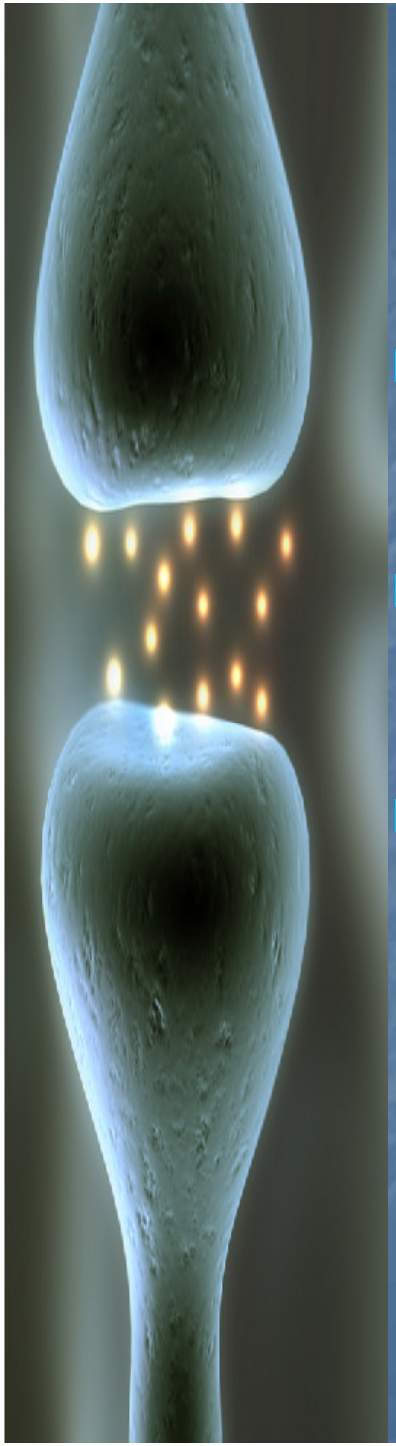
Fuchs-Buder,T. et al. Interaction of magnesium sulphate with vecuronium-induced neuromuscular block. British Journal of Anaesthesia. 1995;74:405-409

What do Magnesium and Ketamine have in common with The Sanford Health-Meritcare Merger ?????

Sanford & MeritCare

Health

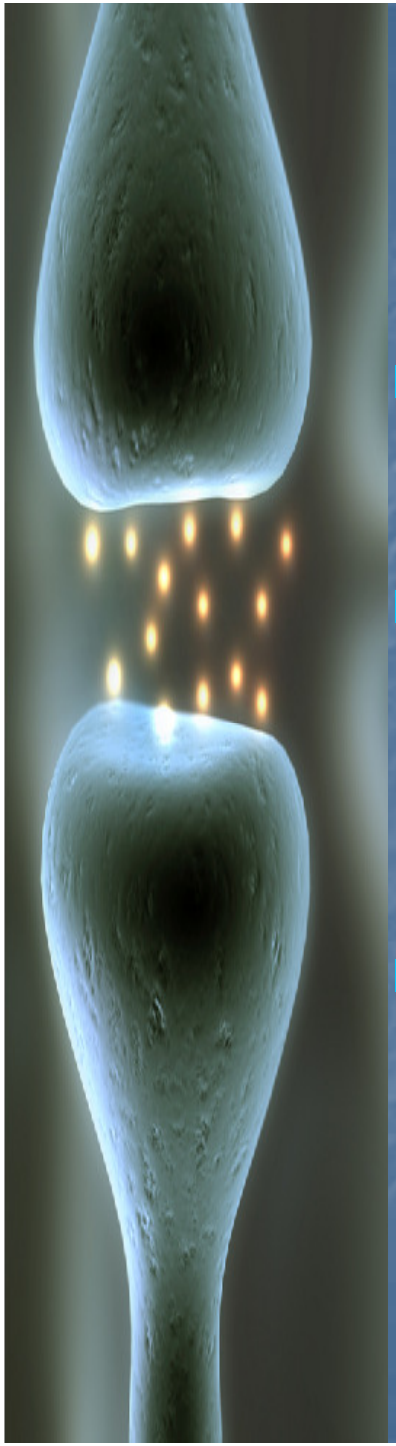
Stronger Together



Ketamine and Magnesium

- Combinations of ketamine and magnesium potentiate each other.
- Combinations are more effective analgesiacs than either alone; thus,
- Superadditive (>90%) effect of coadministration allows for reduced doses of each; thus, less side effects.

Hong-Tao,L et al. Modulation of NMDA Receptor Function by Ketamine and Magnesium: Part I Anesthesia & Analgesia. 2001;92:1173-1181



Ketamine Infusion Dosing THINK SMALL

- Ketamine exerts NMDA effects at subanesthetic levels.
- Analgesic level: 30-120 ng/ml serum

  6 mg/hr/70 kg patient =50ng/ml

  15 mg/hr/70 kg patient =125ng/ml
- Side effects at: >200 ng/ml serum

  25 mg/hr/70 kg patient =200ng/ml

Suzuki,M. Role of N-Methyl-D-aspartate receptor antagonists in postoperative pain management. Current Opinion in Anaesthesiology. 2009;22:619-622

Ketamine Bolus Dosing
Keep THINKing SMALL

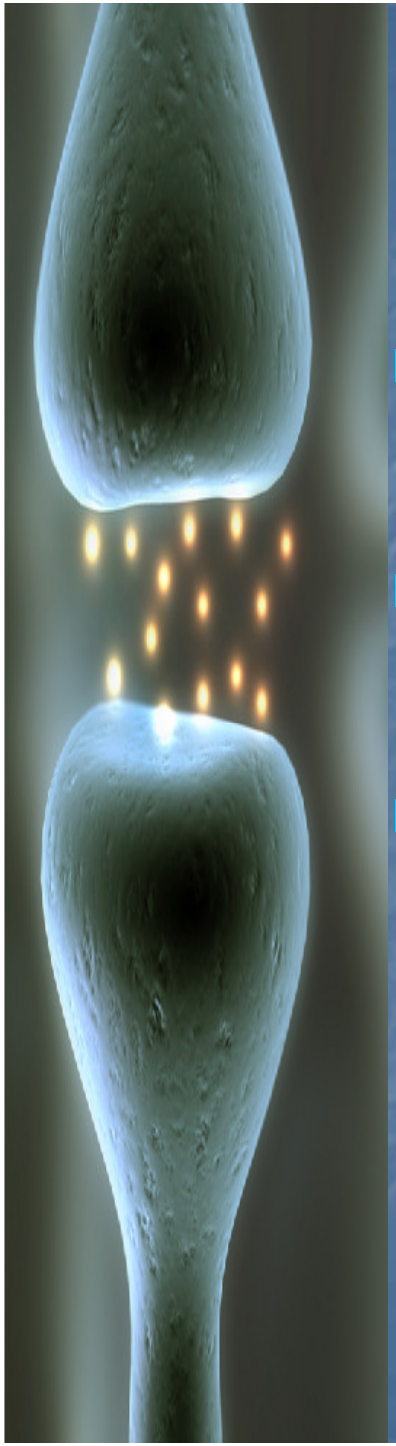
- Of 24 studies reviewed using ketamine, 14 (58%) demonstrated preventive analgesia effects.

- Usual study boluses: 0.15 – 1 mg/kg
  10 – 70 mg / 70kg patient

McCartney,C. et al. A Qualitative Systematic Review of the Role of N-Methyl-D-Aspartate Receptor Antagonists in Preventive Analgesia. Anesthesia and analgesia 2004;98:1385-1400

Ketamine and Magnesium My recipe

- Infuse between induction and incision by combining:
  - 20-30 mg/kg magnesium
  - 0.25mg/kg ketamine
  - Reduce NMB dosing by 25%
  - Repeat if surgery > 2 to 3 hours length.
  - Careful NOT to give magnesium near end of surgery.



Postop PCA Ketamine

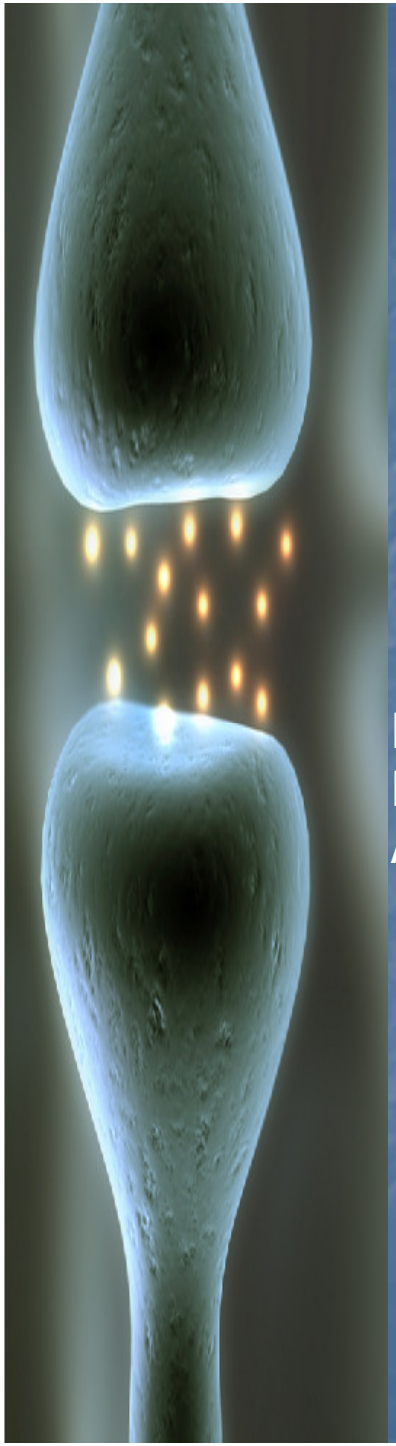
- Often given PCA as 1:1 with Morphine with synergistic effects.
- 60% of studies demonstrate a morphine sparing effect of 45-60%.
- Combination provides a significant decrease in Morphine side effects yet found no increase in psychoto-mimetic effects in 9 of 11 studies

Carstensen, M. & Møller, A.M. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain:A qualitative review of randomized trials. British Journal of Anaesthesia. 2002: 89; 594-598

Dextromethorphan

- Dextromethorphan is a low affinity noncompetitive NMDA antagonist.
- Dextrorphan (its metabolite) has x8 the NMDA affinity.
- Dextrorphan is a phencyclidine like (PCP) compound.

Yueh-Ching,C et al. Binding of dimemorfan to sigma-1 receptor and its anticonvulsant and locomotor effects in mice, compared with dextromethorphan and dextrorphan. Brain Research. 1999; 821:516-519



Dextromethorphan

- Preventive analgesia benefit in 67% of studies.
- Dosed Parenterally at 1 mg/kg (IV or IM) preoperatively (NOT PO)

McCartney,C. et al. A Qualitative Systematic Review of the Role of N-Methyl-D-Aspartate Receptor Antagonists in Preventive Analgesia. Anesthesia and analgesia 2004;98:1385-1400

- Effective as premed adjunct for tonsillectomy and mastectomy

Siu, A & Drachtman,R. Dextromethorphan: A Review of *N*-methyl-d-aspartate Receptor Antagonist in the Management of Pain. CNS Drug Reviews. 2007:13; 96-106

Dextromethorphan-Helmy

- Dextromethorphan has analgesic effect beyond its pharmacologically active period

Table 3.(excerpts) Visual Analogue Scale and Retrospective Verbal Pain Scores

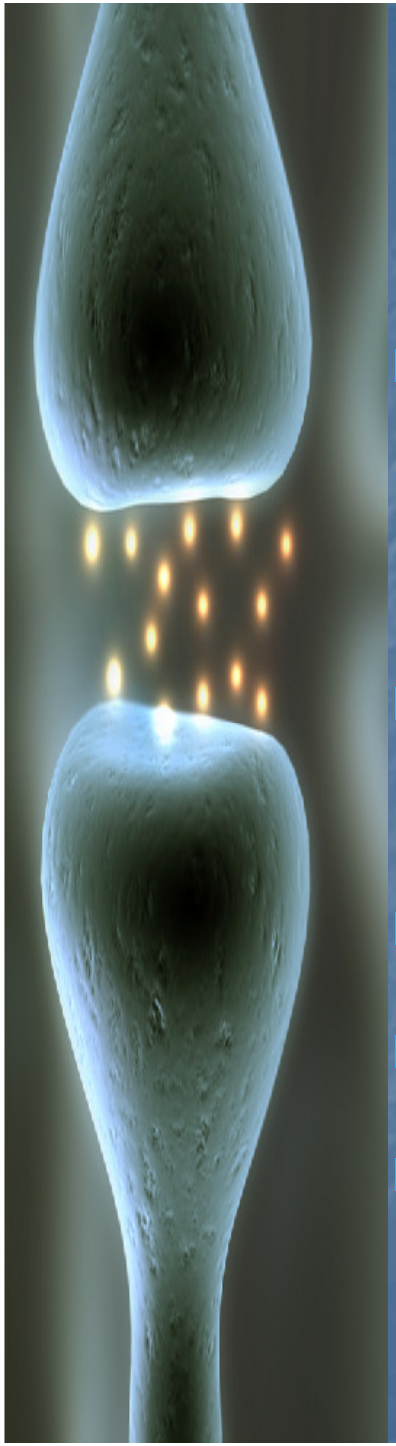
Score Variable	Preincisional Dextromethorph	Postincisional dextromethorphan	Control Group
6-h VAS			
Rest	**13** (0–30)*	**31** (22–50)	**37** (24–42)
Movement	30 (22–43)*	**53** (32–61)	**55** (26–63)
24-h VAS			
Rest	27 (10–31)	35 (17–53)	38 (16–45)
Movement	32 (11–42)	46 (27–58)	44 (27–56)

Helmy,S. & Bali,A The effect of the preemptive us of the NMDA receptor antagonist Dextromethorphan on Postoperative Analgesic Requirements. Anesthesia & Analgesia. 2001; 92:739-44

Dextromethorphan-Helmy

- Helmy treated upper abdominal surgery patients with 120 mg IM DM 30 minutes preincision versus postincision versus placebo.
  - Preincision Tx grp had significantly decreased pain and analgesia requirements postop.
  - PreincisionTx grp also had less hypoxemic events

Helmy,S. & Bali,A The effect of the preemptive us of the NMDA receptor antagonist Dextromethorphan on Postoperative Analgesic Requirements. Anesthesia & Analgesia. 2001; 92:739-44



Methadone

- Mixed isomers
  - S-isomer: a potent MNDA antagonist
  - R-isomer: Potent Mu agonist
- 10-20 minute onset parenterally so it is easy to titrate.
- 24 hour half-life: *Caution for toxicity*
- Load dose 10-20 mg IV
- Excellent drug for patients with opioid abuse, addiction, overuse issues.

Nicotine agonists

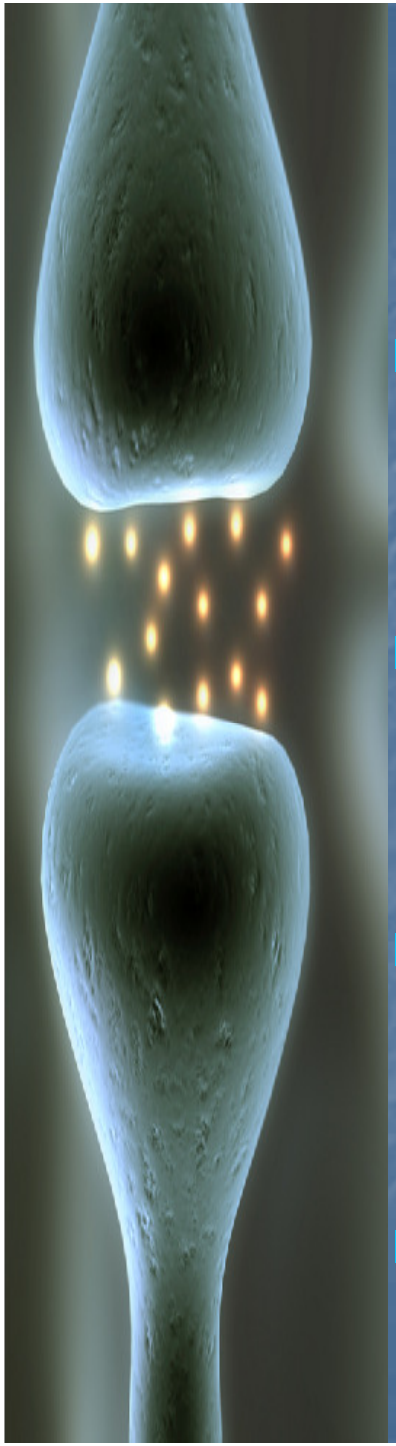
- Nicotine is investigational analgesic
  - Activates preganglionic inhibitory pathways in descending spinal pathways.
  - Less Substance P, Neurokinans and glutamate/glycine released at nerve endings.
  - Thus, less NMDA stimulation.
  - RESULT: Significantly, less post-operative pain and less opioid usage with nicotine agonists.

Nicotine agonists (Flood-2004)

Nicotine nasal spray dose of 3 mg versus NS nasal spray placebo during closure.

- VAS scores Nicotine grp: 4-5
- VAS scores Placebo grp: 7-8
- Analgesic effects last 24 hours despite 45 minute kinetics lifespan of nasal nicotine.

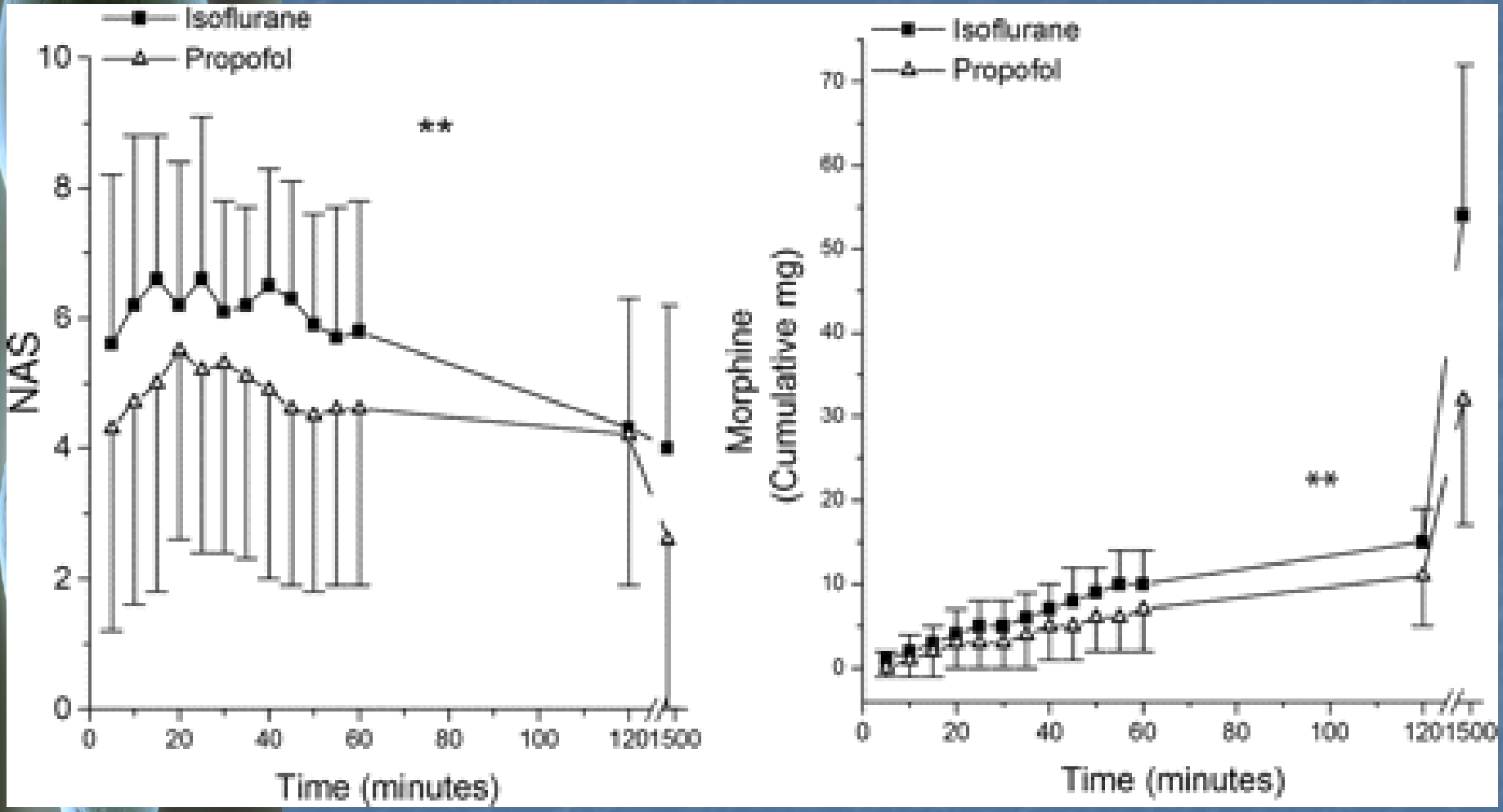
Flood P, Daniel D. Intranasal nicotine for postoperative pain treatment. Anesthesiology. 2004; 101:1417-21



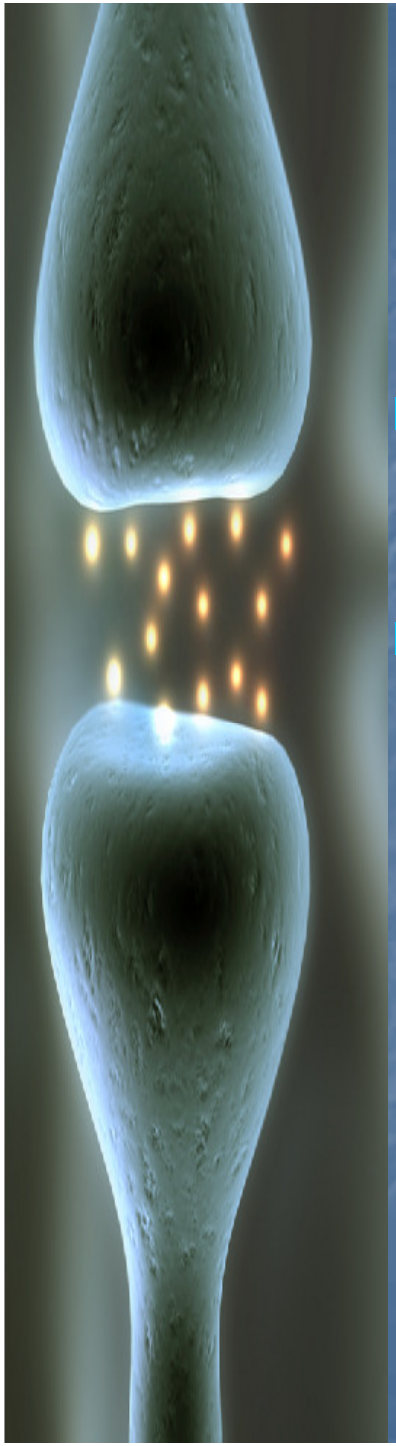
Nicotine agonists (cont)

- No side-effect of increased sympathetic activity as hypothesized (*rather, decreased HR & BP)*
- Does not work on smokers as they seem to be desensitized to nicotine from chronic use
- Nicotine patch is even more effective than nasal spray with VAS scores in PACU of 1-2. (not dose dependent)
- Nicotine agonist drugs currently in development.

Propofol Vs. Inhal agents :Hyperalgesia



Cheng, S. et al. Anesthesia Matters: Patients Anesthetized with Propofol Have Less Postoperative Pain than Those Anesthetized with Isoflurane. Anesthesia & Analgesia. 2008;106(1): 264-269



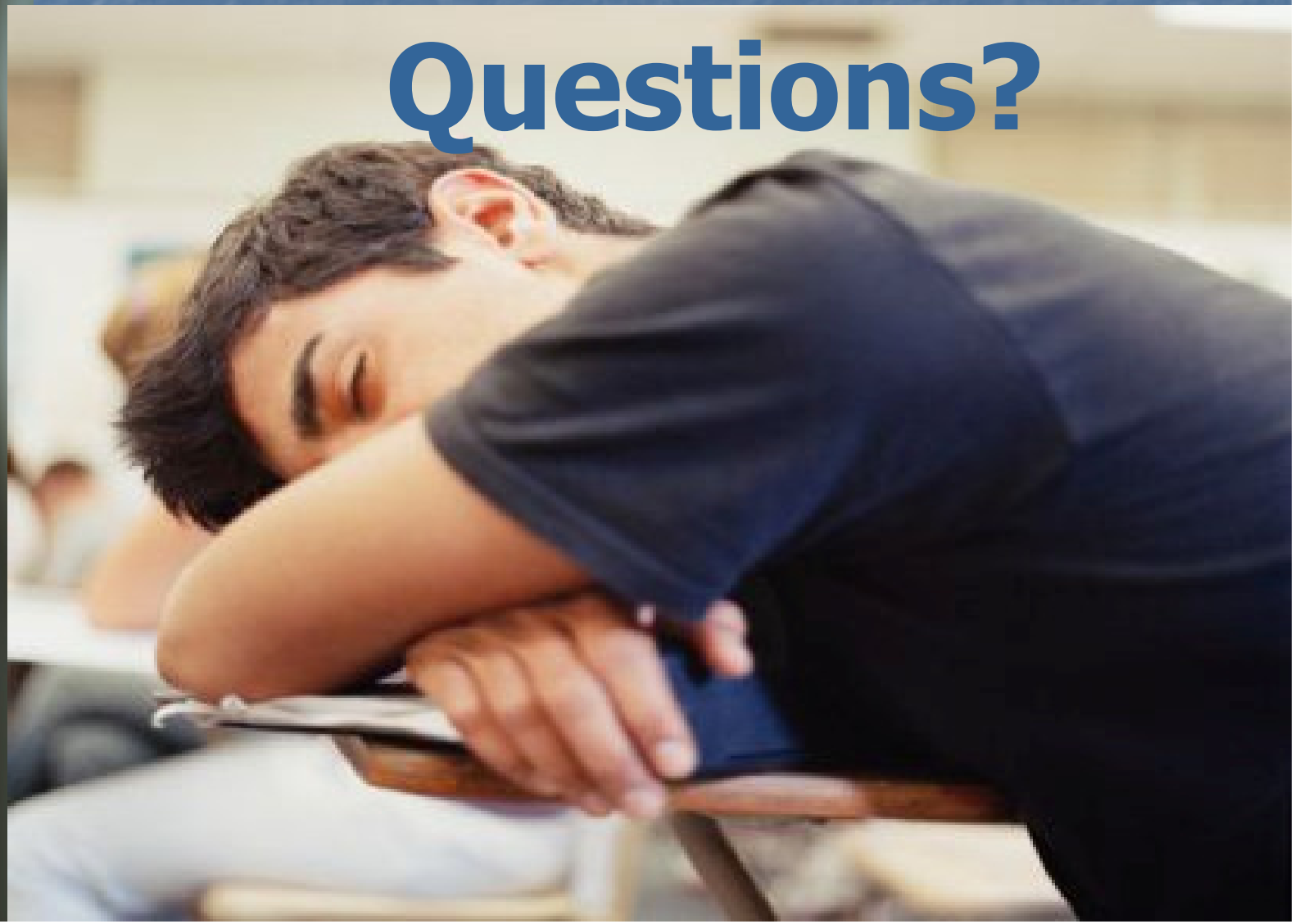
Miscellaneous NMDA antagonists/adjuncts

- Memantine (Namenda) for phantom limb pain
- Antidepressants (esp. TCAs)

Overview

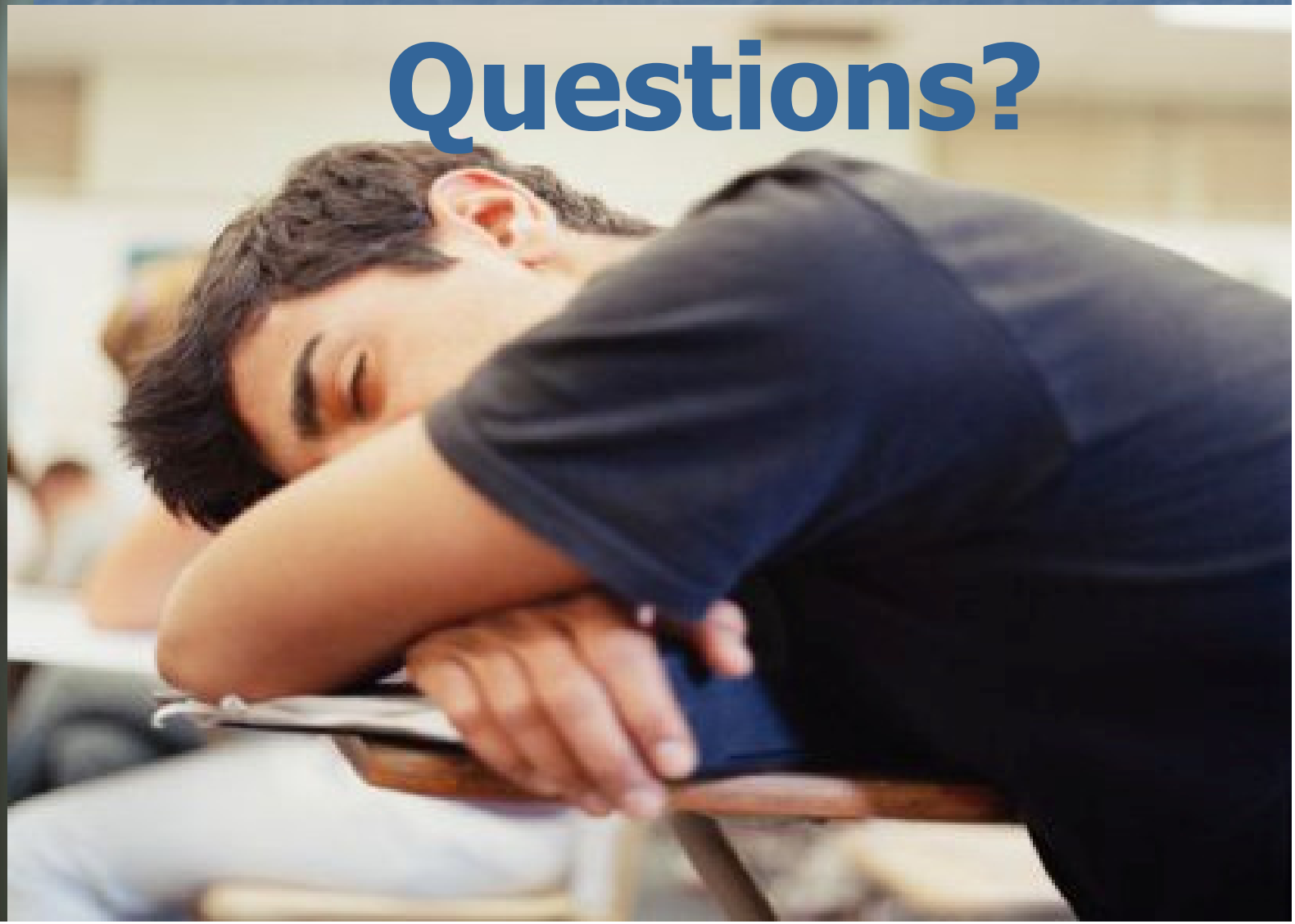
- NMDA activation BAD…
- NMDA antagonism GOOD !!

You've arrived… *or survived*



Questions?

You've arrived… *or survived*



Questions?