Topics in Laboratory Animal Medicine
Anesthesia/Analgesia

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Plan

- Continuing education
- Questions
- Emphasis on injectables
- *Note*: “extra” slides on CD/handout

Disclaimers

- This is not an ACLAM sanctioned presentation
- No information presented is known to be specifically included in ACLAM Board examinations
- All information is deemed reliable and correct
  - (No warranty for accuracy)

Terminology

- **Anesthesia**
- **Analgesia**
- **Sedation**
- **Hypnosis**

- **artificially induced sleep or trance**
- **loss of sensation to body part or whole body**
- **central depression with drowsiness, reduced awareness**
- **loss of sensitivity to pain**

Terminology, con't.

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Terminology, con't.

- Pain: an unpleasant sensory or emotional experience associated with actual or potential tissue damage
- Nociception: peripheral and central nervous system processing of information about the internal or external environment related to tissue damage

(Committee on Pain and Distress in Laboratory Animals, 1992; Flecknell and Waterman-Pearson, 2000)

Terminology, con't.

- General Anesthesia = loss of consciousness in addition to loss of sensation
  - Hypnosis
  - Hyporeflexia
  - Analgesia
  - Muscle relaxation

Terminology, con't.

- Surgical Anesthesia = loss of consciousness and sensation, along with sufficient muscle relaxation and analgesia for painless surgery

According to Antognini et al. (Comp Med 2005), which of the following is NOT a feature of general anesthesia?

A. Amnesia
B. Unconsciousness
C. Immobility
D. Analgesia

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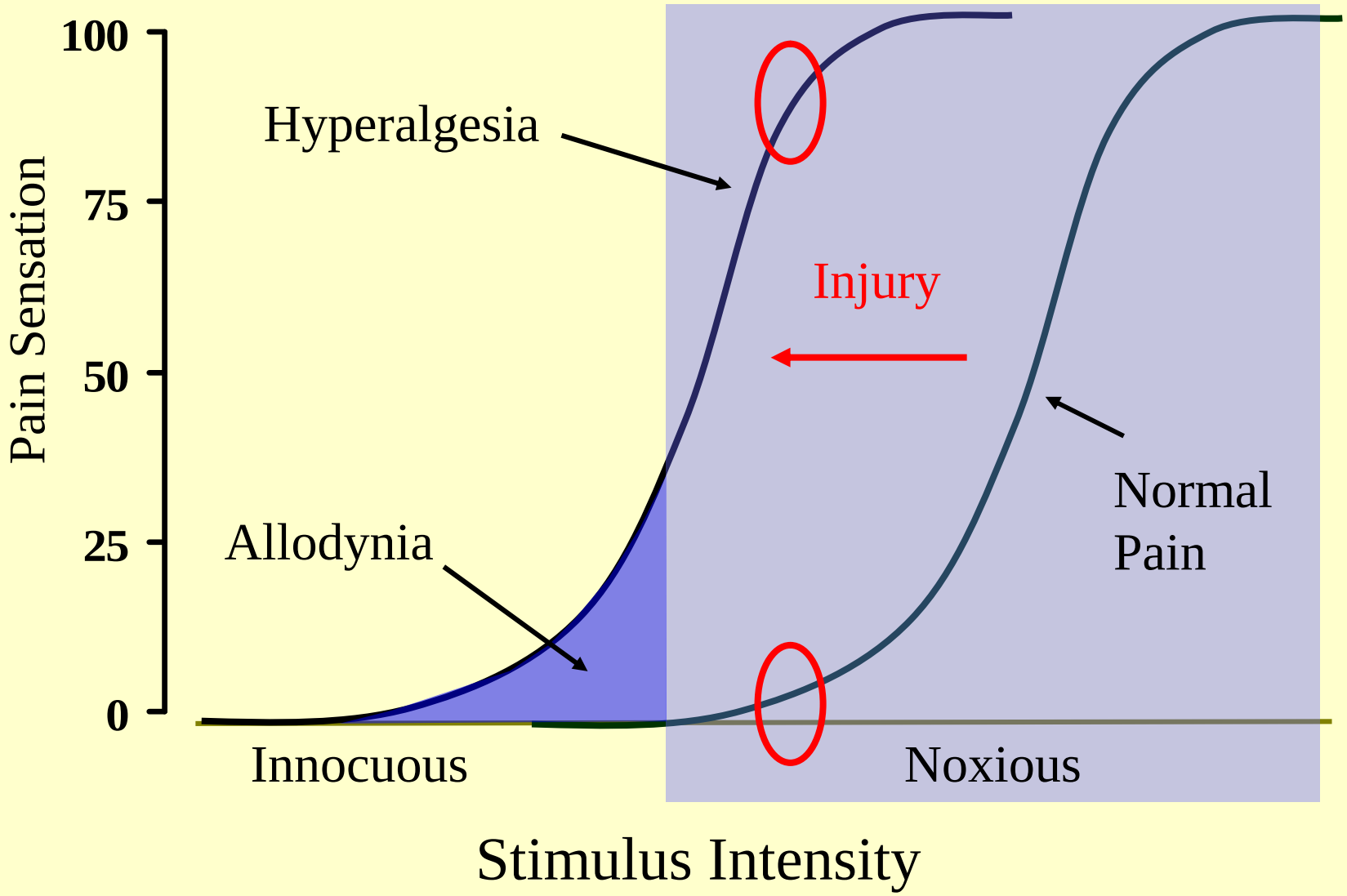
D. Analgesia

Effects of injury on pain sensation

(courtesy: Paul Flecknell)



Which of the following are physiological features of general anesthesia?

A. Respiratory depression
B. Cardiovascular depression
C. Decreased renal function
D. Impaired thermoregulation
E. Hormonal alterations
F. All of the above

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Literature Cautions

TRUE/FALSE: If it's in the literature, it must be true.

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Literature Cautions

- Definitions
  - anesthetic depth/ antinociceptive potency
- Controls/ baselines
- Cardiorespiratory state, body temperature
- Drug effect vs. general anesthesia
- Is one article enough?

Literature Cautions, con't.

- Animal subject variables
  - genotype
  - age
  - sex
  - body composition
  - nutritional/disease state
- Individual variation
- Dosage

Why Injectables?

TRUE/FALSE: Injectable anesthetics are used primarily because they provide general anesthesia of superior quality.

Why Injectables?

TRUE/FALSE: Injectable anesthetics are used primarily because they provide general anesthesia of superior quality.

Why Injectables?

- Default: habit, familiarity
- Decreased equipment
- Difficulty of intubation
- Safety
- Preserve physiological reflexes/cardiorespiratory function

Why Injectables?

- Specific antagonists
- Balanced anesthesia: = ??
  - combination of drugs, each → specific pharmacological effect
    - Tranquilization
    - Hypnosis
    - Analgesia
    - Muscle relaxation
    - Amnesia?
  - N2O + opioid + NMB, +/- sub-MAC inhalant and midazolam
- TIVA: = ??

Injectable "Anesthetics"

- Barbiturates
- (Other) Hypnotics
- Steroids
- Cyclohexamines
- Alpha-2 agonists
- Local anesthetics

- Anesthetic combinations:

  above +/-
  - Opioids
  - Sedatives and tranquilizers

Injectable "Anesthetics"

- Alternative classification based on mechanism of action

TRUE/FALSE: Most injectable anesthetics act at the neuronal cell membranes to alter Na+ permeability.

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- Alternative classification based on mechanism of action

TRUE/FALSE: Most injectable anesthetics act at the neuronal cell membranes to alter Na+ permeability.

Injectable "Anesthetics"

- GABA agonists
- NMDA antagonists
- Alpha2 agonists
- Miscellaneous
- Local anesthetics
- Neuroleptic/antipsychotic agents
- Injectable combinations

Which of the following is NOT a GABA agonist?

A. Ketamine
B. Metomidate
C. Propofol
D. Ethylmethyl thiourea (Inactin)
E. Diazepam

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GABA Agonists

(dose-dependent CNS depressants)

- Barbiturates
- Chloral hydrate
- Alpha chloralose
- Tribromoethanol (Avertin)
- Propofol
- Metomidate and etomidate
- Steroids

Hypnotics – Why Use Them?

- Dose-dependent CNS depressants
  - i.e., sleep
- Convenience
  - single injection (+/-)
  - rapidly metabolized *OR* “long term stable anesthesia”
- Minimal cardiorespiratory depression

TRUE/ FALSE: Chemical grade anesthetics can be used safely for anesthesia if filter-sterilized.

MAYBE: Chemical grade anesthetics can be used safely for anesthesia if filter-sterilized.

Examples?

- Chloralose
- Urethane
- Tribromoethanol
- Inactin

TRUE/ FALSE: Hypnotics in general are poor analgesics.

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Which of the following has been associated with pathologic changes following IP administration?

A. Cloral hydrate
B. Chloralose
C. Urethane
D. Tribromoethanol
E. All of the above

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A. Cloral hydrate
B. Chloralose
C. Urethane
D. Tribromoethanol
E. All of the above

Tribromoethanol

TRUE/ FALSE: TBE is a well-characterized injectable anesthetic used primarily in mice.

Tribromoethanol

TRUE/ FALSE: TBE is a well-characterized injectable anesthetic used primarily in mice.

See:

- RE Meyer and RE Fish. (2005). A review of tribromoethanol anesthesia for production of genetically engineered mice and rats. Lab Anim (NY). 34, 47-52.)
- CC Lieggi et al. (2005). Efficacy and safety of stored and newly prepared tribromoethanol in ICR Mice. Contemp Topics 44(1): 17- , 2005.

TBE – Why DO *We Use It?*

Propofol

TRUE/ FALSE: Because of its formulation, aseptic technique is especially important in the handling of propofol.

Propofol

TRUE/ FALSE: Because of its formulation, aseptic technique is especially important in the handling of propofol.

For which of the following would use of propofol for anesthesia be LEAST appropriate?

A. Dogs
B. Cat
C. Pig
D. Rabbit
E. Rat

For which of the following would use of propofol for anesthesia be LEAST appropriate?

A. Dogs
B. Cat
C. Pig
D. Rabbit
E. Rat

Which of the following can significantly suppress adrenal cortical activity?

A. Ketamine
B. Metomidate
C. Urethane
D. Chloral hydrate

Which of the following can significantly suppress adrenal cortical activity?

A. Ketamine
B. Metomidate *(also etomidate)*
C. Urethane
D. Chloral hydrate

Which if the following best describes alphaxalone/ alphadolone?

A. Barbiturate
B. Local anesthetic
C. Hypnotic
D. NSAID
E. Neuroleptanalgesic

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A. Barbiturate
B. Local anesthetic
C. Hypnotic
D. NSAID
E. Neuroleptanalgesic

aka: anesthetic steroid; “Saffan”

Which of the following is NOT a characteristic of ketamine?

A. NMDA antagonist
B. Cyclohexamine
C. Dissociative anesthetic
D. Sympathomimetic anesthetic
E. Monoanesthetic

Which of the following is not a characteristic of ketamine?

A. NMDA antagonist
B. Cyclohexamine
   (along with phencyclidine, tiletamine)
C. Dissociative anesthetic
D. Sympathomimetic anesthetic
E. Monoanesthetic

Cyclohexamines

TRUE/ FALSE: Although an effective agent for chemical restraint, ketamine is considered a poor analgesic.

Cyclohexamines

TRUE/ FALSE: Although an effective agent for chemical restraint, ketamine is considered a poor analgesic.

Which of the following is NOT an alpha2 adrenoreceptor agonist?

A. Xylazine
B. Detomidine
C. Metomidate
D. Romifidine

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A. Xylazine
B. Detomidine
C. Metomidate
D. Romifidine

don’t confuse with medetomidine

Which of the following is NOT a characteristic of xylazine?

A. Alpha2 agonist
B. Sedative-analgesic, muscle relaxant
C. Sedative/hypnotic
D. Poor analgesic
E. Potency << medetomidine

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A. Alpha2 agonist
B. Sedative-analgesic, muscle relaxant
C. Sedative/hypnotic
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Urethane

TRUE/ FALSE: Urethane refers to a family of polymers ranging from rubbery to brittle; a versatile type of plastic material that can be manufactured into a flexible or rigid sheet, a coating, an ink, or adhesive.

Urethane

TRUE/ FALSE: Urethane refers to a family of polymers ranging from rubbery to brittle; a versatile type of plastic material that can be manufactured into a flexible or rigid sheet, a coating, an ink, or adhesive.

- How does urethane (anesthesia) work?
- Why use urethane?

Which of the following is a carcinogen and mutagen?

A. Chloralose
B. Tribromoethanol
C. Urethane
D. Alphaxalone/alphadolone
E. Ether

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B. Tribromoethanol
C. Urethane
D. Alphaxalone/alphadolone
E. Ether

Opioids

Morphine acts primarily at which receptor?

A. μ
B. δ
C. ε
D. κ
E. σ

Opioids

Morphine acts primarily at which receptor?

A. μ
B. δ
C. ε
D. κ
E. σ

Which of the following is a partial opioid agonist?

A. Buprenorphine
B. Morphine
C. Fentanyl
D. Meperidine
E. Remifentanil

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A. Buprenorphine
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Butorphanol?

Which of the following is a COX-2 selective drug?

A. Acetominophen
B. Flunixin
C. Carprofen
D. Meloxicam
E. None of the above

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A. Acetominophen
B. Flunixin
C. Carprofen
D. Meloxicam
E. None of the above

What is? celecoxib, rofecoxib

Which of the following does NOT have a specific pharmacologic antagonist?

A. Midazolam
B. Fentanyl
C. Medetomidine
D. Ketamine

Which of the following does NOT have a specific pharmacologic antagonist?

A. Midazolam
B. Fentanyl
C. Medetomidine
D. Ketamine

Antagonists

- Midazolam: flumazenil
- Fentanyl: naloxone
- Medetomidine: yohimbine, atipamezole

TRUE/FALSE: Atipamezole is only effective for medetomidine.

Antagonists

- Midazolam: flumazenil
- Fentanyl: naloxone
- Medetomidine: yohimbine, atipamezole

TRUE/FALSE: Atipamezole is only effective for medetomidine.

What's a Neuroleptic?

- agent that → mental calming, decreased response to stimuli, and muscular relaxation.
- aka tranquilizer, ataractic, psychotropic agent
- c/w sedative/antianxiety agent

Which of the following is NOT a butyrophenone?

A. Azaperone
B. Droperidol
C. Acepromazine
D. Fluanisone

Which of the following is NOT a butyrophenone?

A. Azaperone
B. Droperidol
C. Acepromazine *(=phenothiazine)*
D. Fluanisone

Neuroleptics

TRUE/ FALSE: Neuroleptics do not provide analgesia.

Neuroleptics

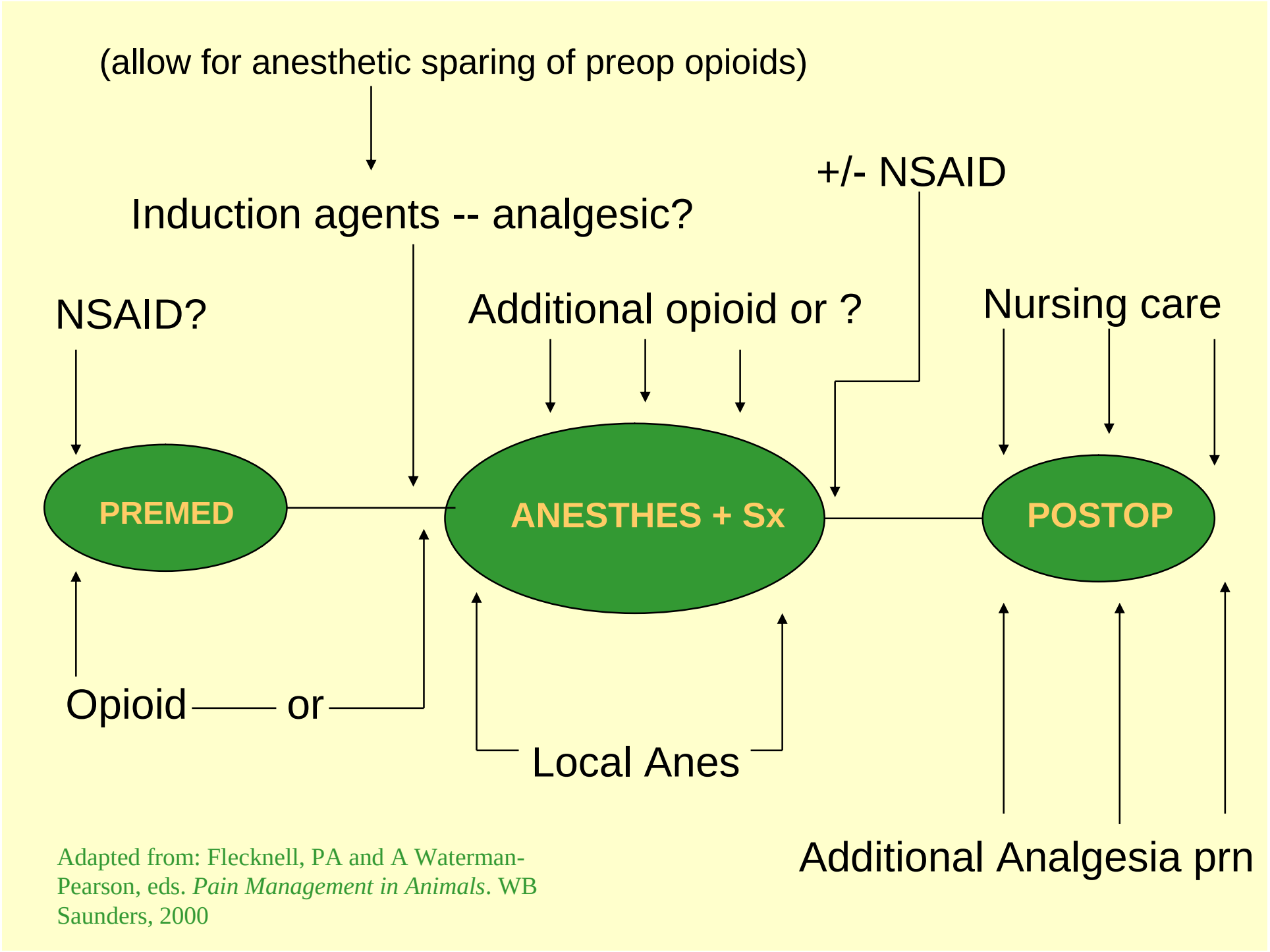
TRUE/ FALSE: Neuroleptics do not provide analgesia.

But…

Injectable Combinations

- Neuroleptanalgesia
  - Innovar (fentanyl/droperidol)
  - Hypnorm (fentanyl/fluanisone)
  - acepromazine/oxymorphone
  - xylazine/butorphanol
- Neuroleptanesthesia
  - neuroleptanalgesia +
- Ketamine combinations (+ xylazine, + medetomidine, + midazolam, + diazepam)
- Tiletamine-zolazepam (Telazol), and TKX
- Etc.

What is multimodal pain therapy?



Adapted from: Flecknell, PA and A Waterman-Pearson, eds. *Pain Management in Animals*. WB Saunders, 2000

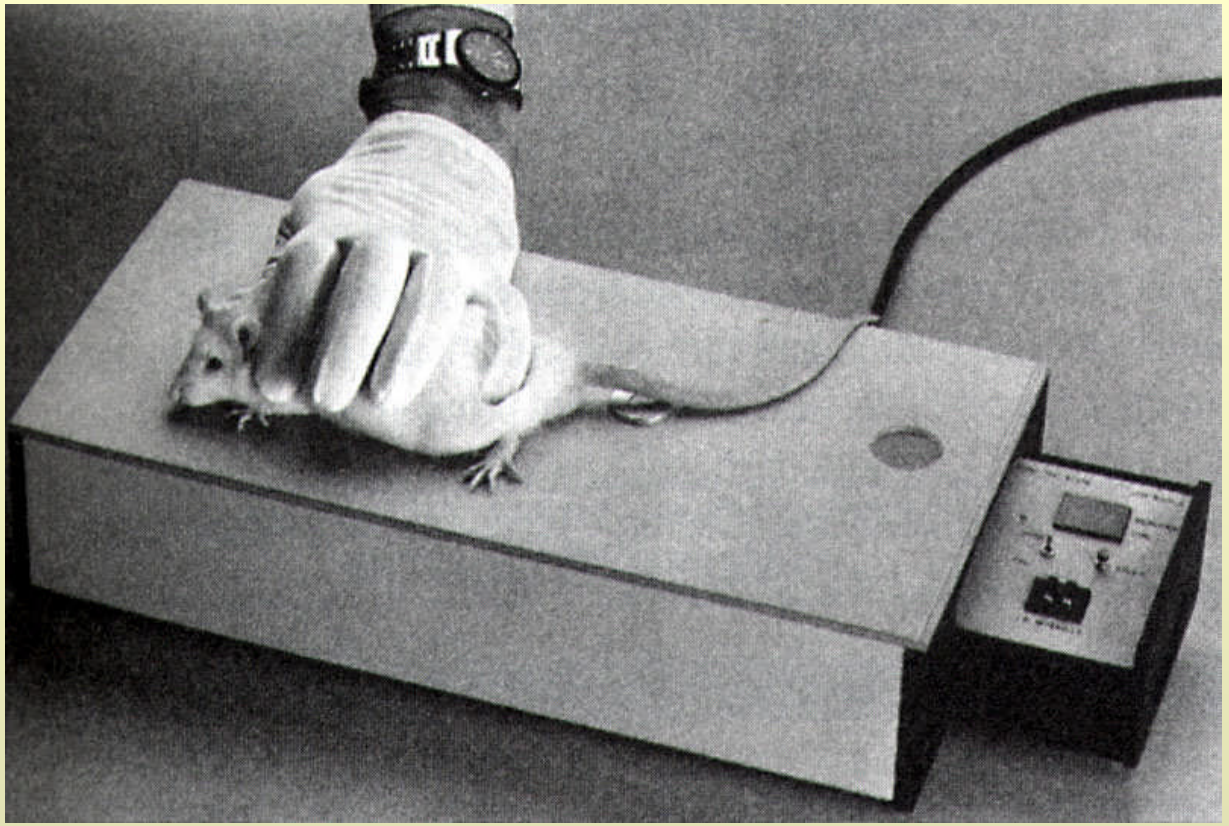
Multimodal pain therapy

- Pre-emptive analgesia
  - → decr. wind-up
  - e.g., ketamine
  - c/w preop ketoprofen, or meloxicam
  - Human studies still controversial
- Alpha-2 agonists
- Local/regional anesthetics

Multimodal pain therapy

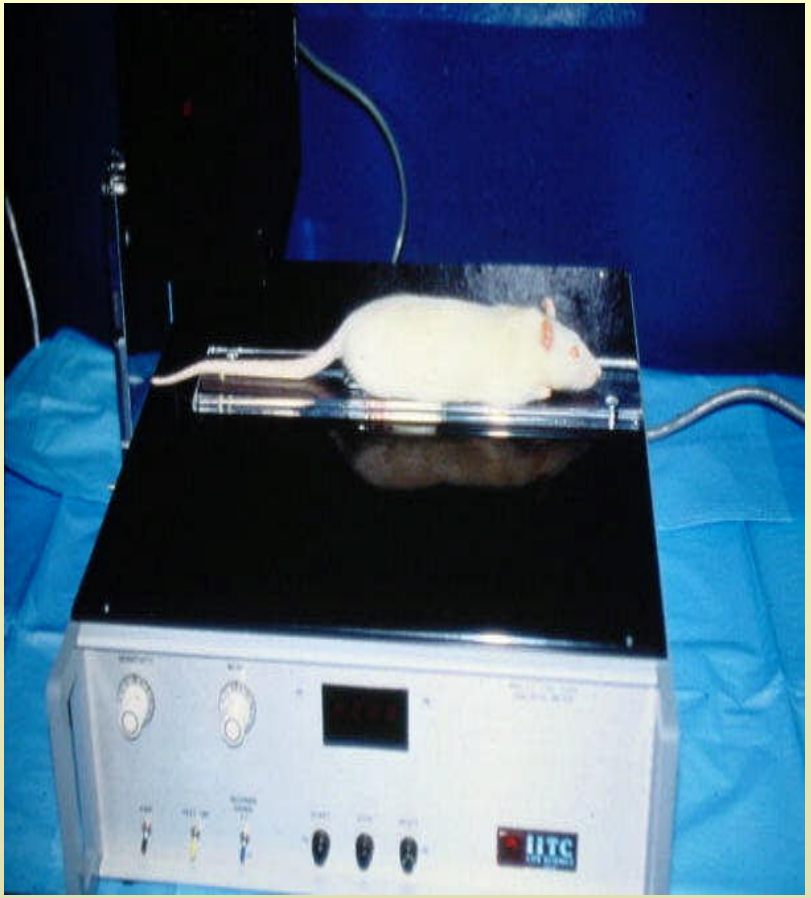
- Opioids (→ extended duration)
  - transdermal fentanyl
  - oral sustained release morphine
  - time release pellets; osmotic pump
  - liposomal preparations

Tail Flick Analgesia Instrument

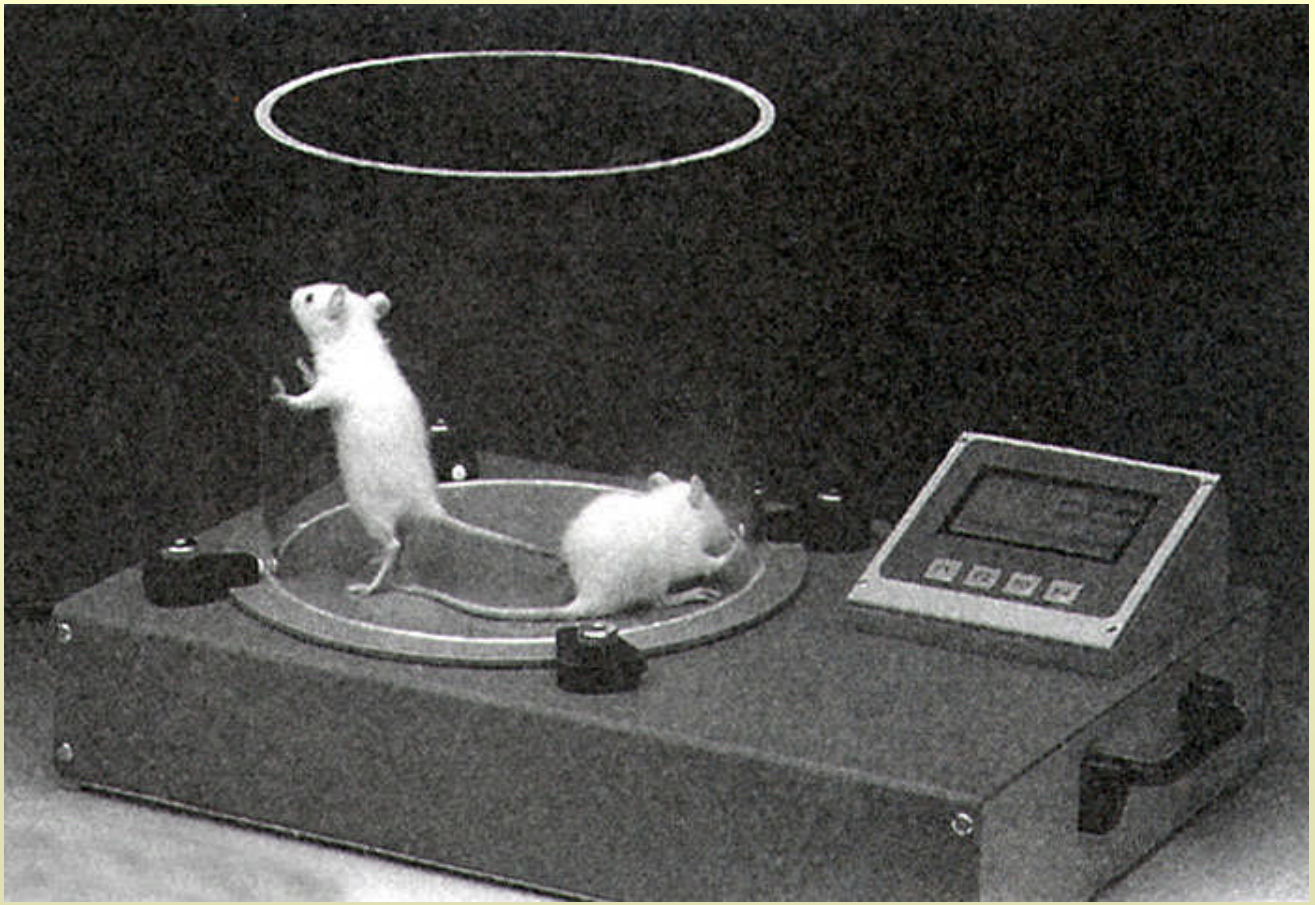


Test for analgesic affects; rodent's tail is placed over window on platform while being restrained. Intense beam of light is applied to the tail (60 – 170^{o} C) and latency period is measured until tail is flicked out of the light beam.

Tail flick (hot)

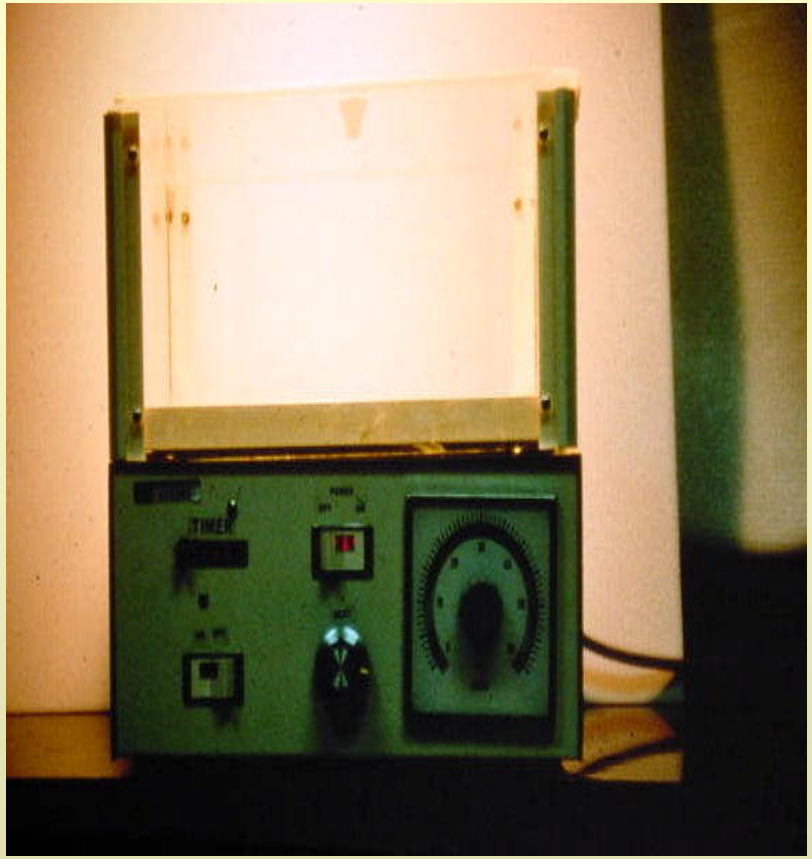


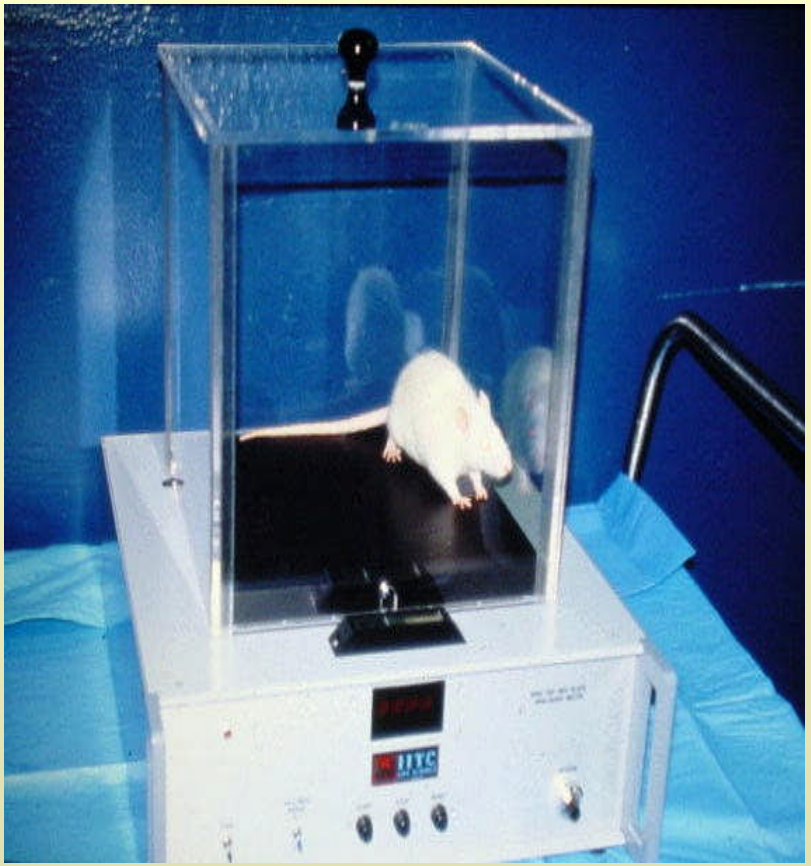
Hot Plate Analgesia Instrument



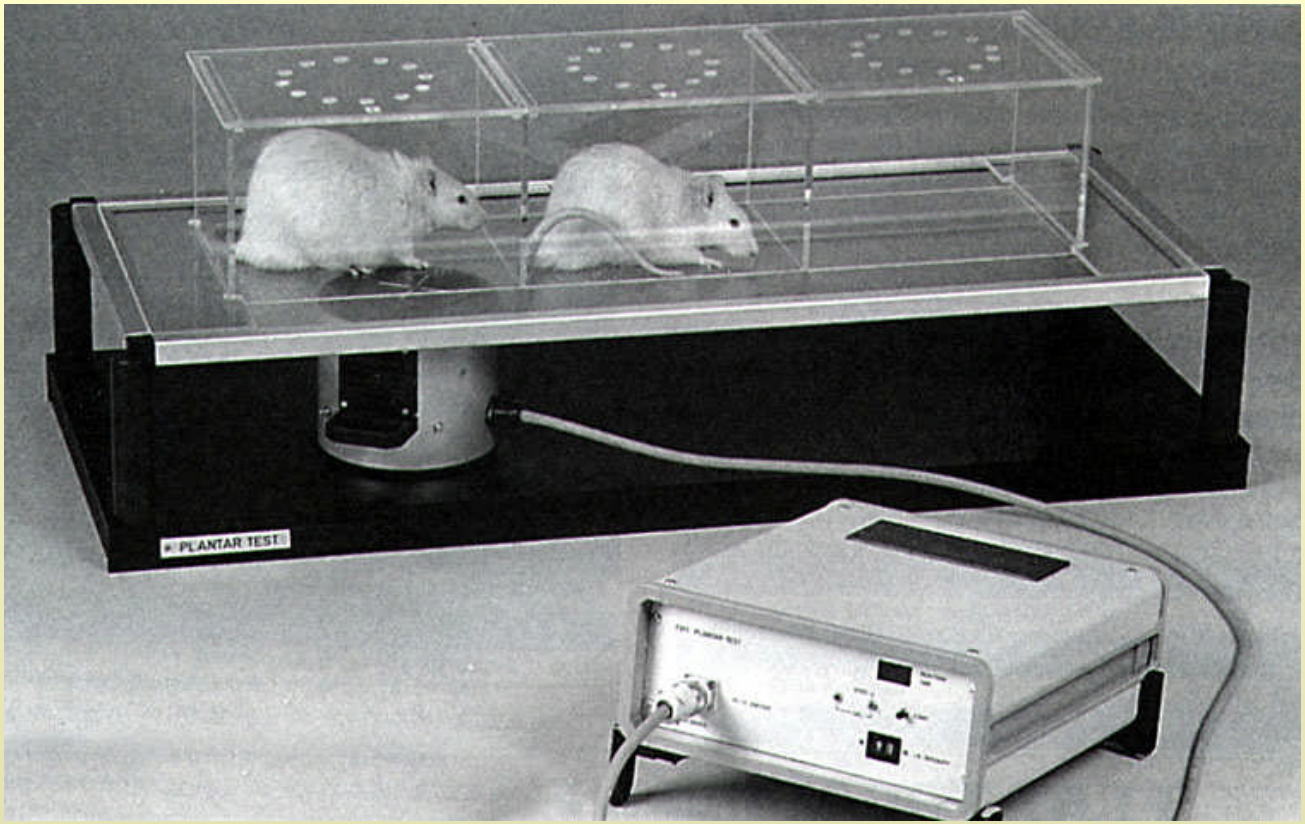
Measures latency of stereotyped paw lick response after dropping mouse or rat onto hot surface (30 – 60º C).

Hot plate





Plantar Analgesia Instrument



Measures paw sensitivity to heat stimulation similar to Hot Plate test, however, animal is unrestrained & heat is applied to bottom of single foot after animal is at rest. Repeated testing does not result in sensitization.

TRUE/ FALSE: Fish feel pain.

http://www.vet.ed.ac.uk/animalwelfare/Fish%20pain/fish%20pain.htm

What is the only FDA-approved anesthetic for use in fish intended for food?

A. Ketamine
B. Pentobarbital
C. Chloral hydrate
D. Isoflurane
E. Tricaine methanesulfonate

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A. Ketamine
B. Pentobarbital
C. Chloral hydrate
D. Isoflurane
E. Tricaine methanesulfonate (MS-222)

What's new with Fish?

- NOT new = MS-222
  - aka tricaine; metacaine; ethyl *m*-aminobenzoate; used as methanesulfonate salt
  - aka Finquel
  - Only FDA-approved anesthetic for use in fish intended for food; 21-day withdrawal
- C/w clove oil
  - Aka eugenol
    - Sladky et al., 2001. AJVR 62(3):337- .

Why Inhalants?

TRUE/FALSE: Inhalants are used primarily for ability to control anesthetic depth.

Why Inhalants?

- Rapid control of anesthetic depth
  - → safety
- Rapid induction and recovery
- Defined (and measurable) level of anesthesia for duration of procedure

Inhalants

TRUE/ FALSE:

MAC = Median anesthetic concentration.

Inhalants

TRUE/ FALSE:

MAC = minimum alveolar concentration.

AGENT	VAPOR PRESSURE	MAC	BLOOD:GAS SOLUBILITY	BIOMETABOLISM (% METABOLITES)
Nitrous oxide	39,500	136-235	0.5	0.004
Diethyl ether	450	3.2	15.2	20
Methoxyflurane	23	0.3	15.0	40-50
Halothane	244	0.8-1.2	2.5	15-20
Enflurane	172	2.2	2.0	2.4
Isoflurane	240	1.2-1.5	1.5	0.2
Sevoflurane	160	2.4-2.5	0.7	3.0
Desflurane	664	5.7-7.1	0.4	0.02

(from Meyer et al., 2002; Brunson (IN Kohn et al.), 1997.)

Inhalants

TRUE/ FALSE: Activated charcoal gas-scavenging units effectively prevent trace levels of isoflurane emissions.

Inhalants

TRUE/ FALSE: Activated charcoal gas-scavenging units effectively prevent trace levels of isoflurane emissions.

- JC Smith et al., 2003. Contemp Topics 42(2): 10- .

The bispectral index is used to help assess which of the following?

A. Pain
B. Distress
C. Anesthesia depth
D. Anxiety
E. Coordination

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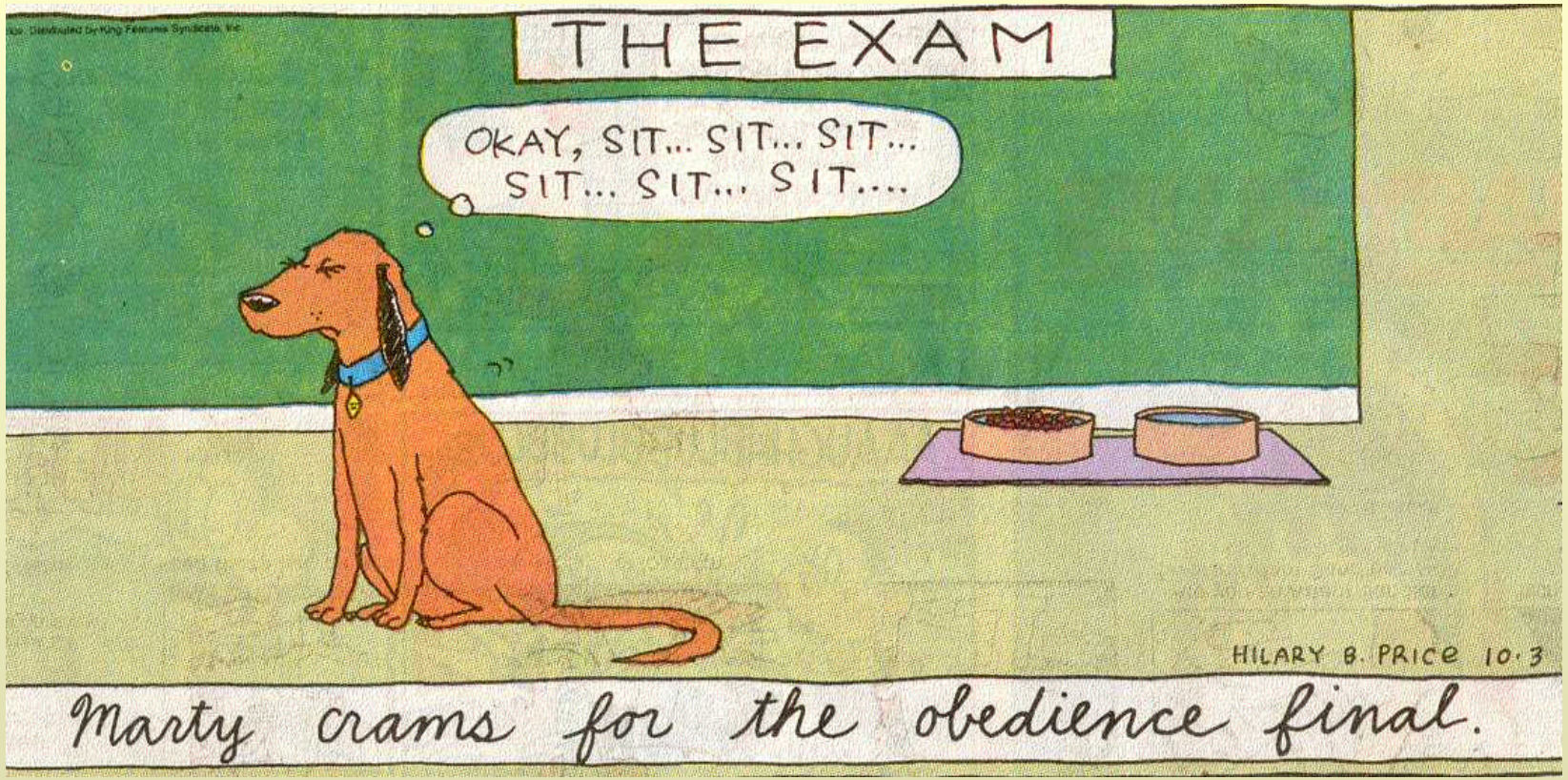

THE EXAM
OKAY, SIT... SIT... SIT... SIT... SIT... SIT....
HILARY B. PRICE 10·3
Marty crams for the obedience final.

Barbiturates

- Description (sedative hypnotic?)
  - Short-acting
    - pentobarbital
  - Ulrashort-acting
    - thiopental, thiamylal, methohexital
  - Inactin (ethylmethyl thiourea (EMTU); thiobutabarbital)

Barbiturates

- Biodisposition
  - species differences in pharmacokinetics
  - pentobarbital metabolism: P450 enzyme system
  - ultrashorts metabolism: redistribution
  - tolerance
  - “barbiturate sleeptime”

Barbiturates

- Pharmacologic effects

  - excitement phase
  - poor analgesia
  - respiratory depression
  - cardiovascular depression
  - arrhythmogenic
  - hypothermia

Barbiturates

- Antagonists
  - no specific pharmacologic antagonists

Chloral Hydrate

- Description
  - trichloroacetaldehyde monohydrate
  - vet use (historical): sedative (cattle, horses)
    - +/- with pentobarb and magnesium sulfate (Equithesin)
  - wide margin of (anesthetic) safety

Chloral Hydrate

- Reported pharmacologic effects
  - minimal analgesia
  - NS effects primarily cerebrum → minimal cardiorespiratory depression
  - irritating to stomach mucosa, perivascular tissue
  - hemolysis, hematuria (IV)
  - adynamic ileus (IP)

Alpha Chloralose

- Description
  - anhydrous chloral + glucose → chloralose
  - solubilized by heat (60 C) or mix w/ urethane
  - long duration hypnosis w/ minimal effect on reflexes

Alpha Chloralose

- Reported phamacologic effects
  - minimal analgesia; poor anesthetic
  - minimal/ transient cardiorespiratory depression
  - minimal effect on autonomic reflex activity (?)
  - IP administration → inflammatory response

Hypnotics

Tribromoethanol

- Description
  - rapid induction, short term surgical anesthesia, rapid recovery
    - → common use in transgenic procedures
  - conflicting reports on efficacy and safety
  - non-pharmaceutical grade powder
  - safe use requires proper preparation and storage
  - pharmacology ??

Tribromoethanol

- Reported pharmacologic effects
  - generalized CNS depression
  - cardiorespiratory depression at increased dosage
  - analgesia?
  - postanesthetic complications
    - decomposition products +/or decreased pH
    - increased dosage
    - repeated use

Propofol

- Description
  - 2,6-diisopropylphenol
  - chemically distinct from barbiturates, steroids, imidazoles
  - oil solubilized with emulsion
  - anesthetic properties similar to thiopental
  - i.v administration

Propofol

- Description
- Biodisposition
  - rapid distribution
  - extensive redistribution
  - rapid hepatic clearance
  - minimal cumulative effects
- Mechanism of action
- Reported pharmacologic effects

Propofol

- Description
- Biodisposition
- Mechanism of action
  - enhanced central GABAergic transmission
  - acts at GABA-A receptor
  - specific site distinct from barbiturates, steroids, benzodiazepines
- Reported pharmacologic effects

Propofol

- Reported pharmacologic effects
  - poor analgesia
  - apnea
  - hypotension; other cardiovascular effects variable

Hypnotics

Metomidate and Etomidate

- Description
  - carboxylated imidazoles
  - long-term anesthesia; minimal cumulative effect
  - metomidate used in variety of spp.; etomidate mostly human

Metomidate and Etomidate

- Description
- Biodisposition
  - IV admin → rapid distribution
  - rapid metabolism in liver; urine excretion
- Mechanism of action
- Reported pharmacologic effects

Metomidate and Etomidate

- Description
- Biodisposition
- Mechanism of action
  - GABA-mimetic
  - actions similar to pentobarb, alphaxalone
- Reported pharmacologic effects

Metomidate and Etomidate

- Reported pharmacologic effects
  - minimal analgesia in larger animals
  - minimal cardiorespiratory depression
  - inhibits adrenal steroidogenesis
  - potential side-effects

Anaesthetic Steroids

(alphaxalone/alphadolone)--key points

- UK-licensed for cats, nonhuman primates
- Rapid induction/recovery; short-term anesthesia; wide safety margin
- Mechanism: GABA-A receptor
- Minimal respiratory depression
- +/- hypotension

Urethane

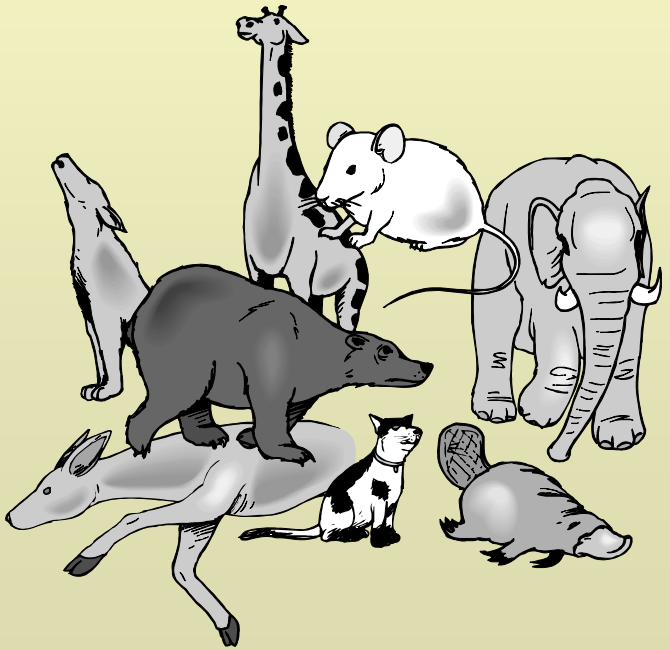
- Description
  - ethyl carbamate
  - soluble in water, alcohol, lipids
  - long duration, wide safety margin
  - rel minor effects on neurotransmission

Urethane

- Reported pharmacologic effects
  - minimal cardiorespiratory depression
  - increased circulating catecholamines
  - IP administration → peritoneal effusion
  - *carcinogenic, mutagenic, immunosuppressive*

Cyclohexamines

- phencyclidine
- ketamine
- tiletamine



Cyclohexamines

- Description
  - dissociative anesthetics
  - sympathomimetic anesthetics
  - wide margin of safety + compatibility with other drugs → wide use
  - Tiletamine + zolazepam → Telazol

Cyclohexamines

- Description
- Biodisposition
  - rapid induction
  - rapid return to consciousness d/t redistribution
  - hepatic cytochrome P450 metabolism
  - renal excretion
- Mechanism of action
- Reported pharmacologic effects

Cyclohexamines

- Reported pharmacologic effects
  - good analgesia, esp musculoskeletal
  - increased cerebral blood flow, intracranial pressure
  - seizure potential (but species dependent)
  - minimal respiratory depression (dose-dependent)
  - hemodynamic stability or stimulation
  - muscle necrosis

Alpha-2 Agonists

- xylazine
- medetomidine
- detomidine

Alpha-2 Agonists

- Description
  - thiazole or imidazole derivative
  - sedative-analgesics, muscle relaxants; anesthetics?
  - potency: xylazine << medetomidine ~= detomidine

Alpha-2 Agonists

- Description
- Biodisposition
  - rapid absorption
  - rapid elimination
  - extensive hepatic metabolism
  - redistribution
- Mechanism of action
- Reported pharmacologic effects
- Antagonists

Alpha-2 Agonists

- Reported pharmacologic effects
  - potent analgesic
  - minimal respiratory depression
  - hypotension, bradycardia, arrythmias
  - hypothermia
  - peripheral agonist effects

Sedatives and Tranquilizers

- Phenothiazines
  - acepromazine
- Butyrophenones
  - droperidol
  - azaperone
  - fluanisone
- Benzodiazepines
  - diazepam
  - midazolam
  - zolazepam

Phenothiazines and Butyrophenones -- key points

- Dose-dependent spectrum of activity:
  - sedation, drowsiness → ataxia, somnolence → cataleptic
- No analgesia, but…
- Side effects, including hypotension

Benzodiazepines -- key points

- Human use: sedative, hypnotic, anxiolytic, muscle relaxant, anticonvulsant
- Tranquilizing effects in animals species-variable
- Elimination T-1/2 in animals much shorter than human
- No analgesia
- Minimal cardiorespiratory depression
- Antagonist: flumazenil

Opioids

- Agonists
  - morphine
  - oxymorphone
  - fentanyl
- Mixed agonist/antagonists
  - butorphanol
  - nalbuphine
- Partial agonists
  - buprenorphine

Injectable Combinations

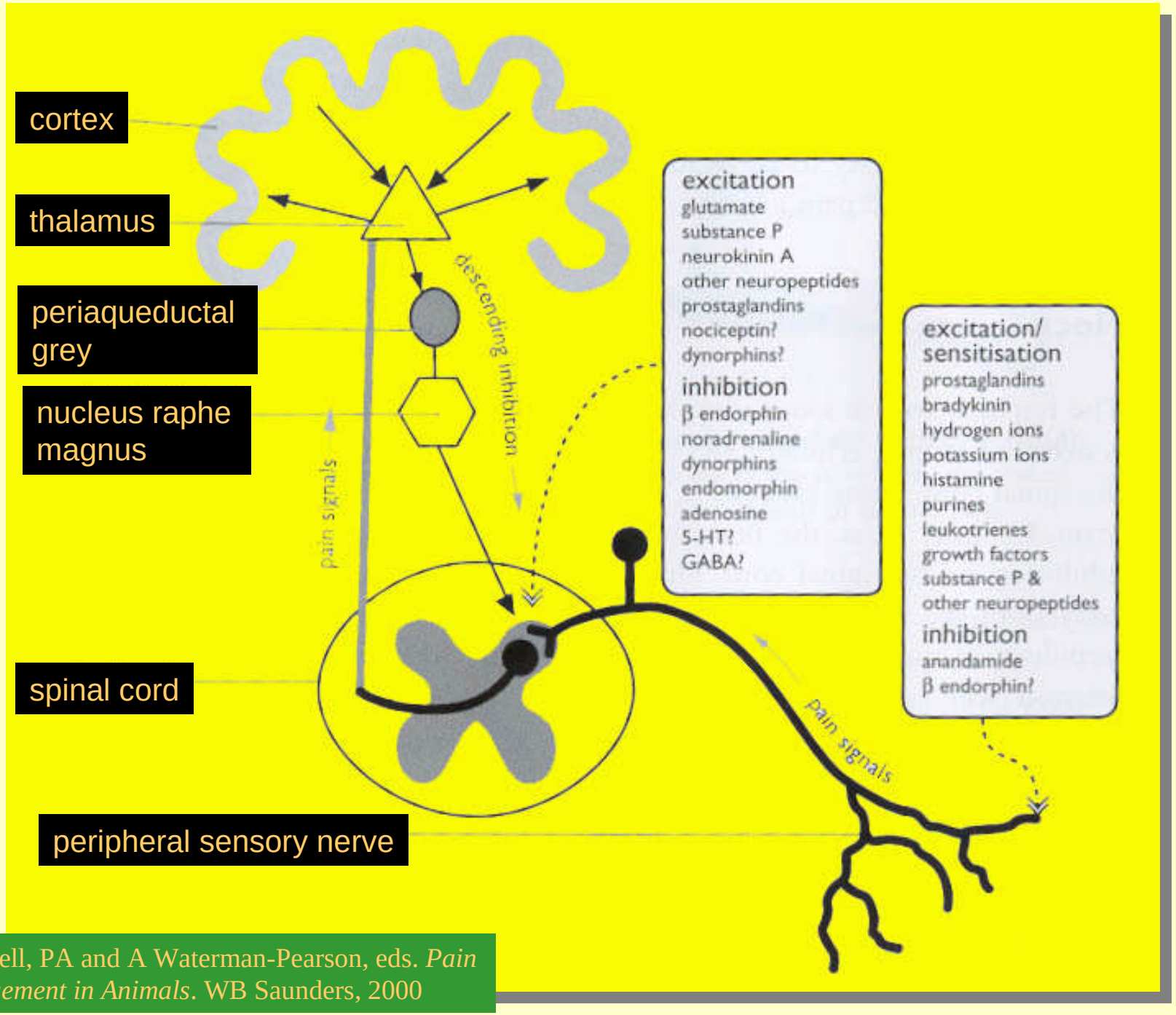
- Tribromoethanol-Medetomidine Combination Provides a Safe and Reversible Anesthetic Effect in Sprague-Dawley Rats.
  - C Gopalan et al. Contemp Topics 44(1):7- , 2005
- Etc.

Search for the Perfect Anesthetic

- Elimination not dependent on metabolism
- Rapid induction, recovery, and change in depth
- Minimal cardiopulmonary depression
- Non-irritant
- Inexpensive, stable, nonflammable, non-explosive
- No special equipment
- Reversible

What's New?

- Equipment – General
  - Matthews, NS, ed. Clinical Anesthesia. Vet Clin N Am/ Sm Anim Prac 29(3), May, 1999.
- Equipment – laryngeal mask airway
  - JC Smith et al., 2004. Contemp Topics 43(4):22- .
- Anesthetic monitoring (e.g., BIS)
  - JE Heavner, 2001. Compar Med 51(6):500- .
  - SA Greene et al., 2002. Compar Med 52(5):424- .
  - SA Greene et al., 2004. Compar Med 54(4):397- .



Flecknell, PA and A Waterman-Pearson, eds. *Pain Management in Animals*. WB Saunders, 2000

Substances affecting transmission of pain signals -- Dorsal Horn

- Excitation
  - glutamtae
  - substance P
  - neurokinin A
  - other neuropeptides
  - prostagalndins
  - nociceptin (?)
  - dynorphins (?)

- Inhibition
  - B endorphin
  - noradrenaline
  - dynorphins
  - endomorphin
  - adenosine
  - 5HT (?)
  - GABA (?)

Substances affecting transmission of pain signals -- Nerve Ending

- Excitation/ Sensitisation
  - prostaglandins
  - bradykinin
  - hydrogen ions
  - potassium ions
  - histamine
  - purines
  - leukotrienes
  - growth factors
  - substance P
- Inhibition
  - anandamide
  - B endorphin (?)

Multimodal pain therapy

- Buprenorphine?
  - Roughan and Flecknell, 2002. Buprenorphine: a reappraisal of its antinociceptive effects and therapeutic use in alleviating post-operative pain in animals. Laboratory Animals, 36, 322-343.

Inhalants

- Cardiovascular differences
  - All are vasodilators, but halothane more cardiodepressant
  - Halothane sensitizes myocardium to catecholamines