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**
  - artificially induced sleep or trance

- **Analgesia**
  - loss of sensation to body part or whole body

- **Sedation**
  - central depression with drowsiness, reduced awareness

- **Hypnosis**
  - loss of sensitivity to pain
Terminology, con’t.

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  - loss of sensitivity to pain
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)
• 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
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
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
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
TRUE/FALSE: If it’s in the literature, it must be true.
TRUE/FALSE: If it’s in the literature, it must be true.
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
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 $\rightarrow$ 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.
Injectable “Anesthetics”

• 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
Which of the following is NOT a GABA agonist?

A. Ketamine
B. Metomidate
C. Propofol
D. Ethylmethyl thiourea (Inactin)
E. Diazepam
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.
TRUE/ FALSE: Hypnotics in general are poor analgesics.
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
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
**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:

TBE – Why DO We Use It?
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
Which if the following best describes alphaxalone/ alphadolone?

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. Cyclohexamime  
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
Which of the following is NOT an alpha2 adrenoreceptor agonist?

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
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
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
Which of the following is a carcinogen and mutagen?

A. Chloralose
B. Tribromoethanol
C. Urethane
D. Alphaxalone/alphadolone
E. Ether
Morphine acts primarily at which receptor?

A. $\mu$
B. $\delta$
C. $\varepsilon$
D. $\kappa$
E. $\sigma$
Opioids

Morphine acts primarily at which receptor?

A. $\mu$
B. $\delta$
C. $\epsilon$
D. $\kappa$
E. $\sigma$
Which of the following is a partial opioid agonist?

A. Buprenorphine
B. Morphine
C. Fentanyl
D. Meperidine
E. Remifentanil
Which of the following is a partial opioid agonist?

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

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

A. Acetaminophen  
B. Flunixin  
C. Carprofen  
D. Meloxicam  
E. None of the above
Which of the following is a COX-2 selective drug?

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/oxymorphine
  - xylazine/butorphanol

- Neuroleptanesthesia
  - neuroleptanalgesia +

- Ketamine combinations (+ xylazine, + medetomidine, + midazolam, + diazepam)

- Tiletamine-zolazepam (Telazol), and TKX

- Etc.
What is multimodal pain therapy?
(allow for anesthetic sparing of preop opioids)

Induction agents -- analgesic?

Additional opioid or ?

Additional Analgesia prn

Nursing care

NSAID?

Opioid or

Local Anes

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° 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 – 60° 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
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 (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
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.
<table>
<thead>
<tr>
<th>AGENT</th>
<th>VAPOR PRESSURE</th>
<th>MAC</th>
<th>BLOOD:GAS SOLUBILITY</th>
<th>BIOMETABOLISM (%METABOLITES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide</td>
<td>39,500</td>
<td>136-235</td>
<td>0.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>450</td>
<td>3.2</td>
<td>15.2</td>
<td>20</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>23</td>
<td>0.3</td>
<td>15.0</td>
<td>40-50</td>
</tr>
<tr>
<td>Halothane</td>
<td>244</td>
<td>0.8-1.2</td>
<td>2.5</td>
<td>15-20</td>
</tr>
<tr>
<td>Enflurane</td>
<td>172</td>
<td>2.2</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>240</td>
<td>1.2-1.5</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>160</td>
<td>2.4-2.5</td>
<td>0.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Desflurane</td>
<td>664</td>
<td>5.7-7.1</td>
<td>0.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

(from Meyer et al., 2002; Brunson (IN Kohn et al.), 1997.)
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
The bispectral index [BIS] is used to help assess which of the following?

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

Okay, sit... sit... sit... sit... sit... sit....

Marty crams for the obedience final.
Barbiturates

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

• Biodisposition
  – species differences in pharmacokinetics
  – pentobarbital metabolism: P450 enzyme system
  – ultrashort metabolism: redistribution
  – tolerance
  – “barbiturate sleeptime”
Barbiturates

- Pharmacologic effects
- excitement phase
- poor analgesia
- respiratory depression
- cardiovascular depression
- arrhythmogenic
- hypothermia
Barbiturates

• Antagonists
  – no specific pharmacologic antagonists
Hypnotics

Chlortal Hydrate

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

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

• Reported pharmacologic effects
Alpha Chloralose

**Description**

- anhydrous chloral + glucose $\rightarrow$ chloralose
- solubilized by heat (60 C) or mix w/ urethane
- long duration hypnosis w/ minimal effect on reflexes
Alpha Chloralose

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

• Reported pharmacologic effects
**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 ??
Hypnotics

**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

- 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, arrhythmias
  – 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

• Equipment – laryngeal mask airway
  – JC Smith et al., 2004. Contemp Topics 43(4):22-.

• Anesthetic monitoring (e.g., BIS)
peripheral sensory nerve
spinal cord
nucleus raphe magnus
periaqueductal grey
thalamus
cortex

excitation
- glutamate
- substance P
- neurokinin A
- other neuropeptides
- prostaglandins
- nociceptin?
- dynorphins?

inhibition
- β endorphin
- noradrenaline
- dynorphins
- endomorphin
- adenosine
- S-HT?
- GABA?

excitation/sensitisation
- prostaglandins
- bradykinin
- hydrogen ions
- potassium ions
- histamine
- purines
- leukotrienes
- growth factors
- substance P & other neuropeptides

inhibition
- anandamide
- β endorphin?
Substances affecting transmission of pain signals -- Dorsal Horn

- **Excitation**
  - glutamtae
  - substance P
  - neurokinin A
  - other neuropeptides
  - prostaglandins
  - 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?
Inhalants

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