PAIN MANAGEMENT IN FOOD-PRODUCING ANIMALS

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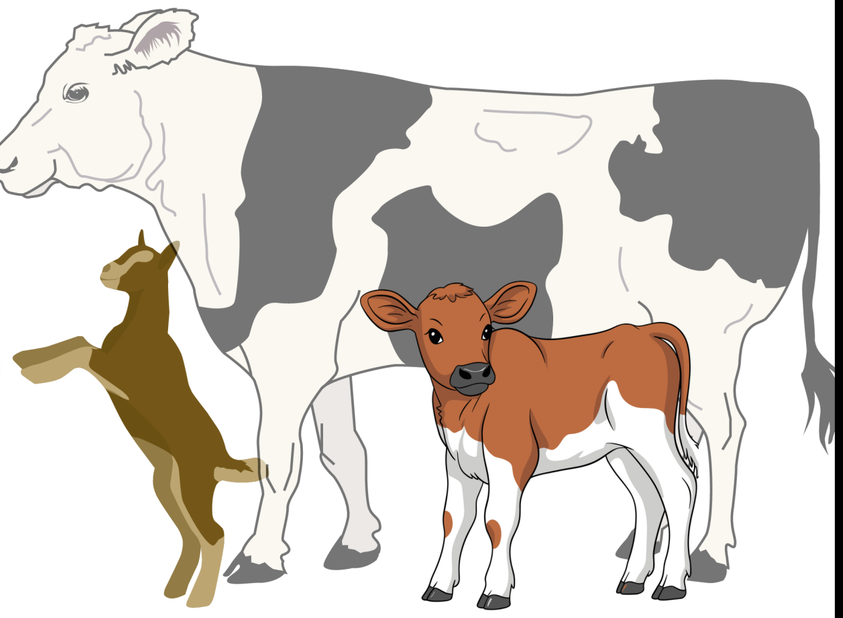


LEARNING OBJECTIVES

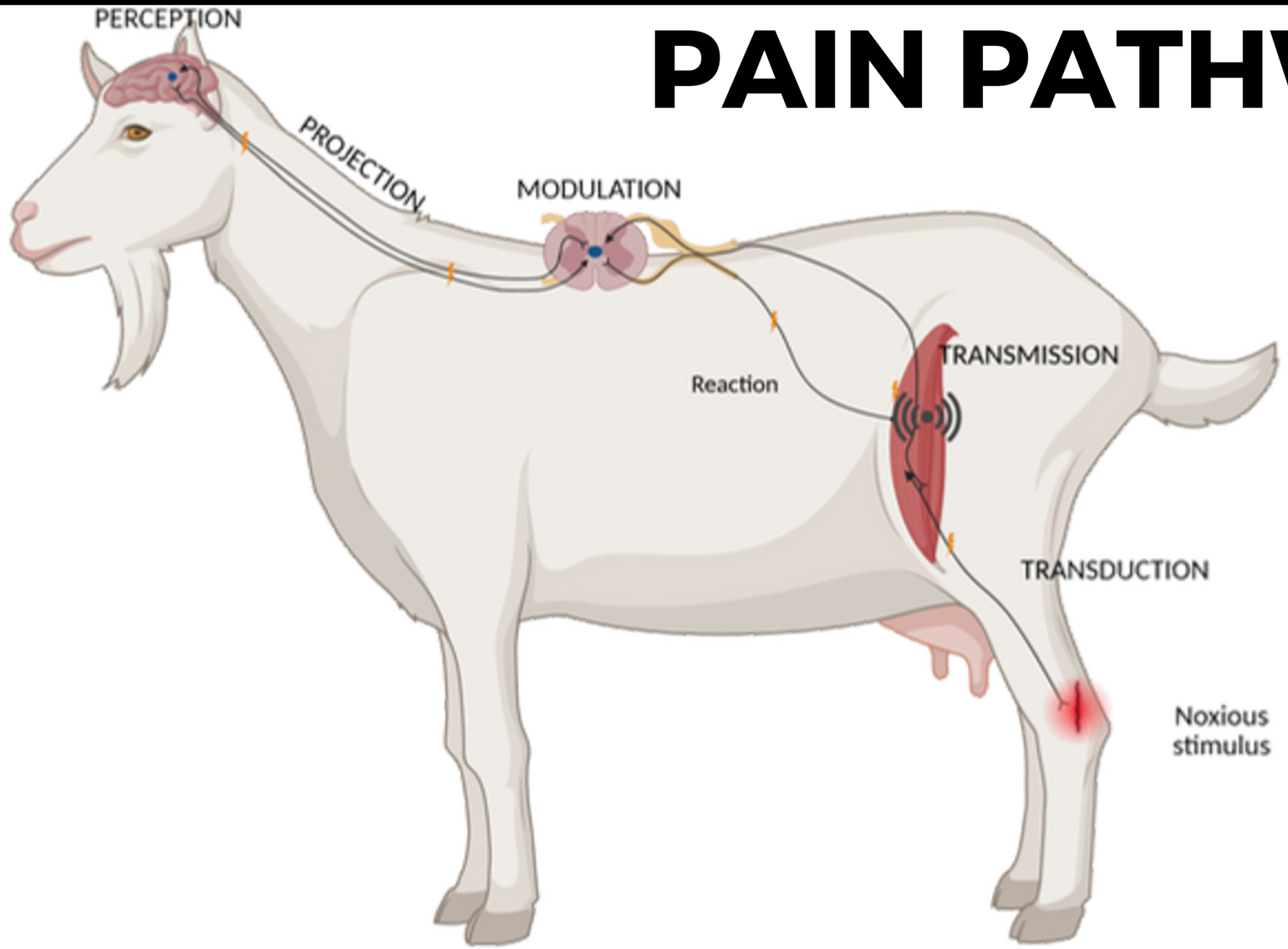
At the end of the lecture, attendees should be able to:

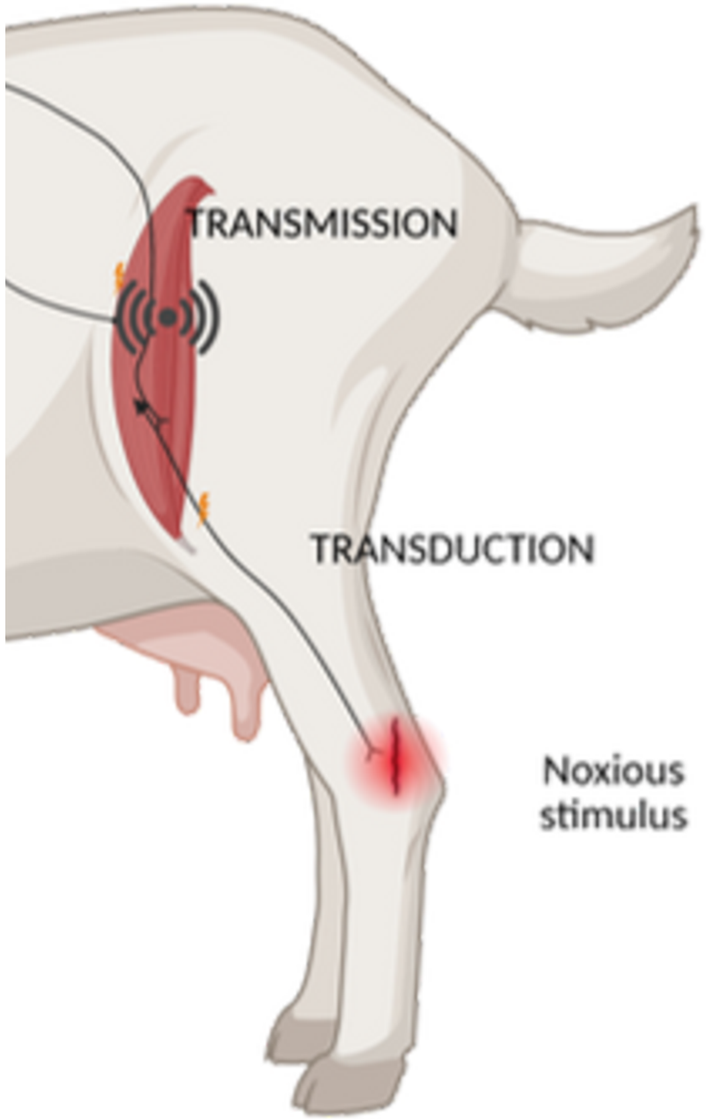
1. Review pain pathway and pathophysiology
2. Describe drugs used for analgesia in food producing species
3. Discuss regulatory concerns and identify species-specific considerations

PHYSIOLOGY OF PAIN

Definition of Pain: "An unpleasant sensory and **EMOTIONAL** experience (A perception) that elicits protective motor actions, resulting in learned avoidance, and is capable of modifying species-specific behavior, including social behavior.

PAIN PATHWAY



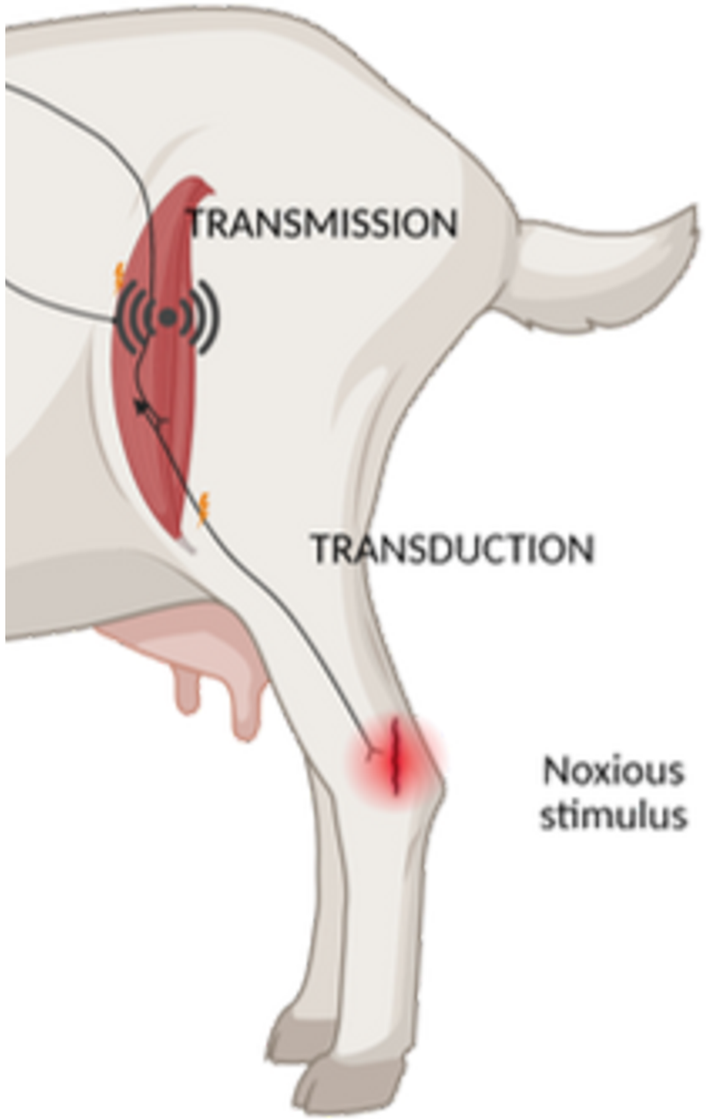


TRANSDUCTION

- Occurs when signaling molecules (**cytokines, bradykinin, and prostaglandins**) are released in response to a noxious stimulus, are converted into an action potential capable of travelling to the central nervous system

Drugs that work on transduction:

- Local anesthesia, Regional anesthesia, Opioids, Alpha-2-agonists, NSAIDs

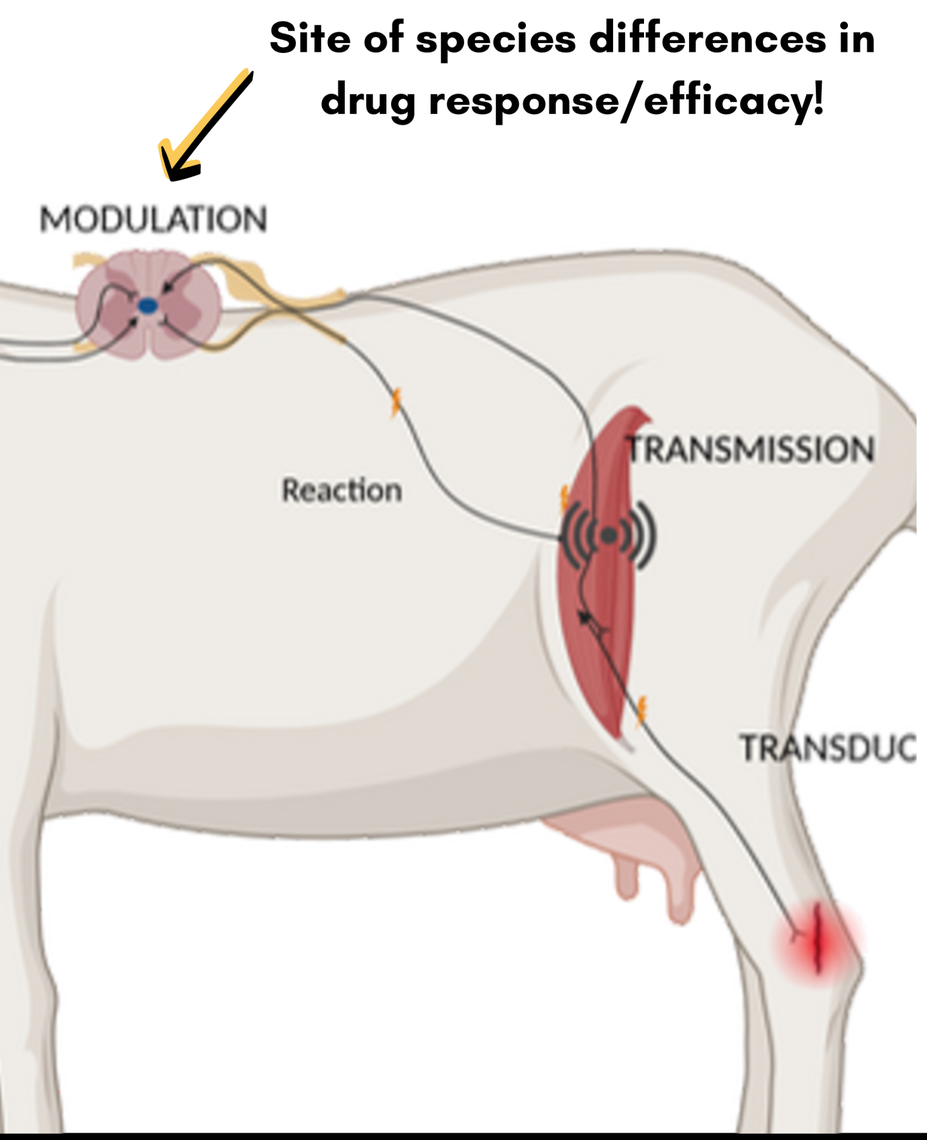


TRANSMISSION

- Follows when this action potential generated during transduction travels to the spinal cord via the **dorsal nerve roots**. It then synapses within the dorsal horn or may be propagated up the spinal cord via the ascending pathway

Drugs that work on transduction:

- Local anesthesia, Regional anesthesia

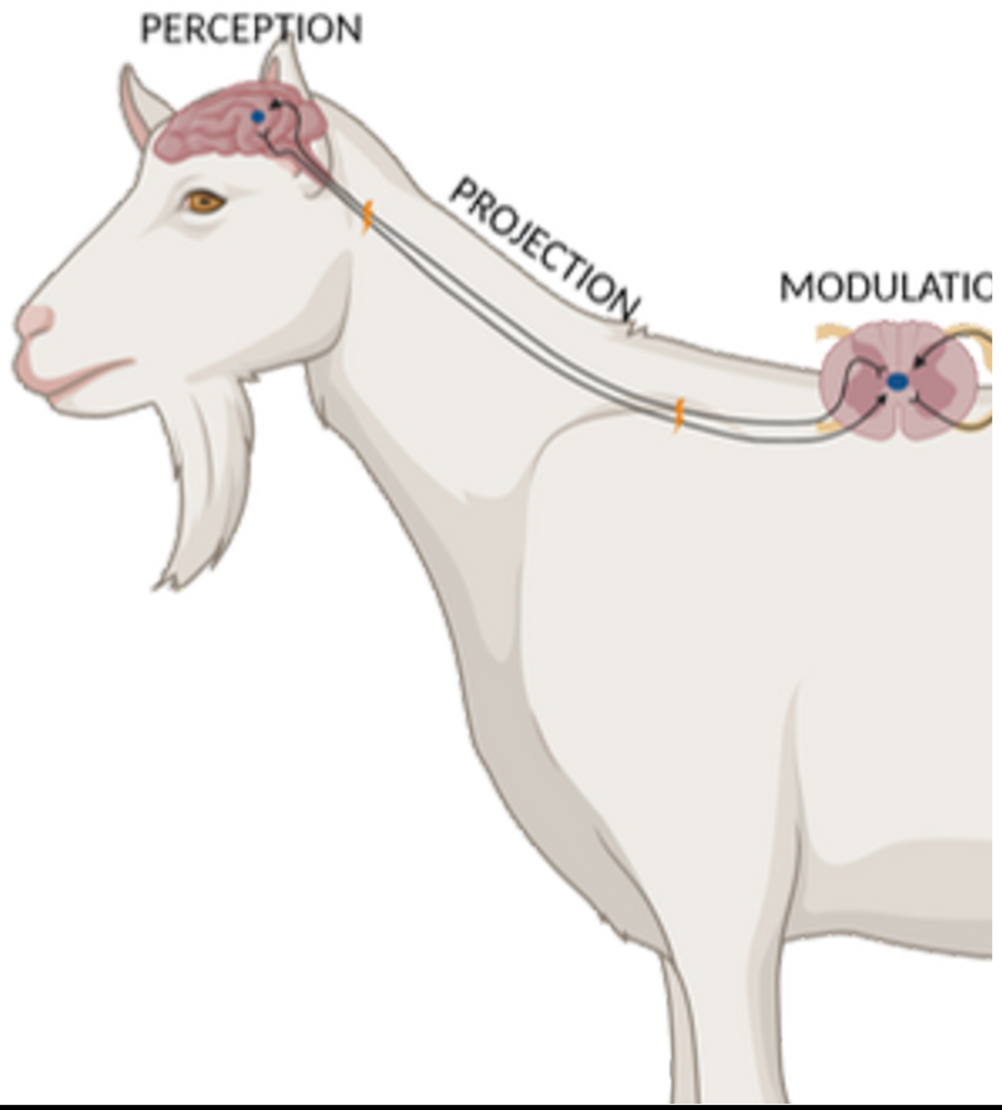


MODULATION

- Process whereby pain transmission is suppressed or heightened via **inhibitory and excitatory mechanisms** in both the peripheral and central nervous systems.

Drugs that work on transduction:

- NSAIDs, Opioids, Local anesthesia, alpha-2-agonists, dissociative anesthetics



PERCEPTION

- Pain is experienced when the signal is perceived in the higher centers of the brain.

Drugs that work on transduction:

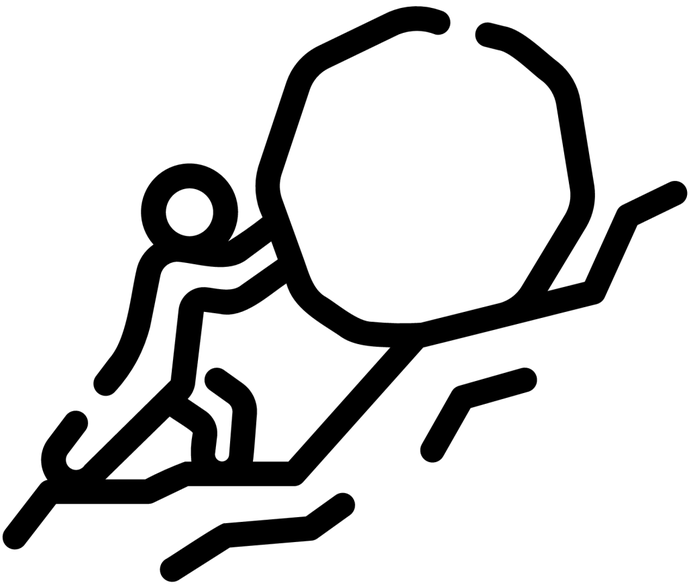
- NSAIDs, Opioids, Injectable anesthetics, sedatives

IDEAL ANALGESIC

- Non sedating
- Long duration of action
- Convenient route of administration
- Economically priced
    - **Cost of therapy < Value of Animal x Prognosis**

CHALLENGES

- Lack of recognition of signs of pain
- Withdrawal periods
- Lack of products
- Economics



RECOGNITION OF PAIN

- Altered function – Non-weight bearing on a limb
- Fearful behaviors – “Flight” response
- Reduced apetite – Anorexia

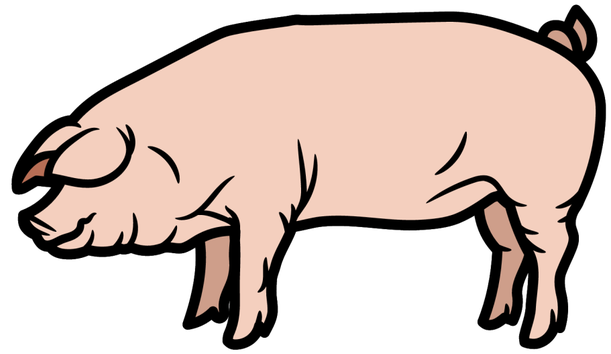
Problem with this – A significant amount of pain is likely already present!

RECOGNITION OF PAIN

- **Ruminant Specific:**
  - Anorexia
  - Hunched appearance
    - Visceral Pain
  - Bruxism or “Teeth Grinding”

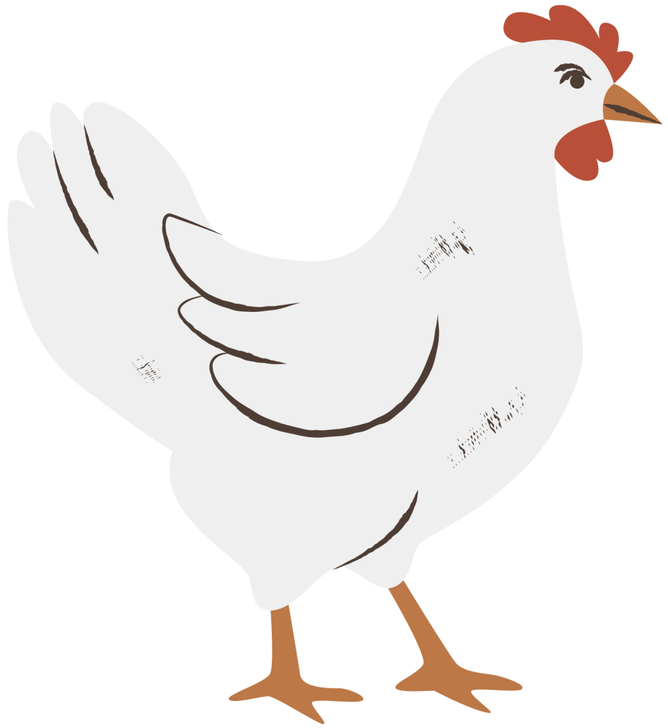
RECOGNITION OF PAIN

- **Swine Specific:**
  - Posture and gait, such as an abnormal walk, stiffness, or reluctance to move
  - Social isolation or lying apart from other pigs
  - Decreased appetite
  - Abnormal vocalizations



RECOGNITION OF PAIN

- **Poultry Specific:**
  - Hunched posture
  - Ruffled feathers
  - Head tucked in
  - Dropped wings
  - Closed eyes
  - Reduced activity



MEASUREMENT OF PAIN

- Pain Scores/Scales
- Substance P
- Prostaglandins
- Mechanical Nociceptive threshhold
- Cortisol

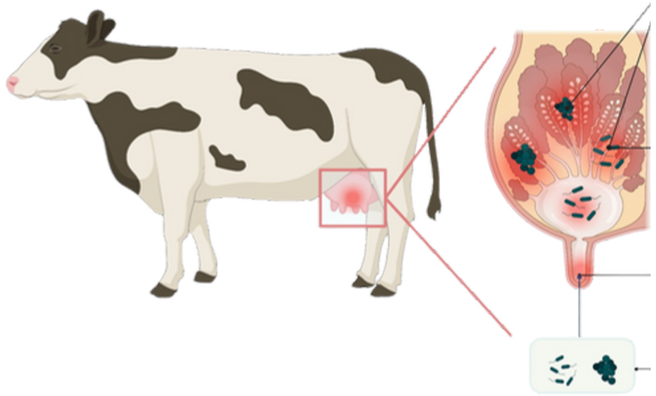
Problem with this - Not “stall side” or clinically measurable for general practitioners

AVAILABLE ANALGESICS

- **Local Anesthetics:**
  - Lidocaine
  - Bupivicaine
  - Procaine
- **Non-Steroidal Anti-inflammatory Drugs**
  - Flunixin meglumine
  - Meloxicam
  - Firocoxib
  - Ketoprofen
- **Opioids**
  - Morphine
  - Butorphanol
- **Dissociative**
  - Ketamine
- **Alpha-2-agonists**
  - Xylazine
  - Dexmedetomidine

NSAIDS

Cardinal Clinical Signs of Inflammation



- **Acute Inflammation as 5 cardinal signs:**
  - Redness
  - Heat

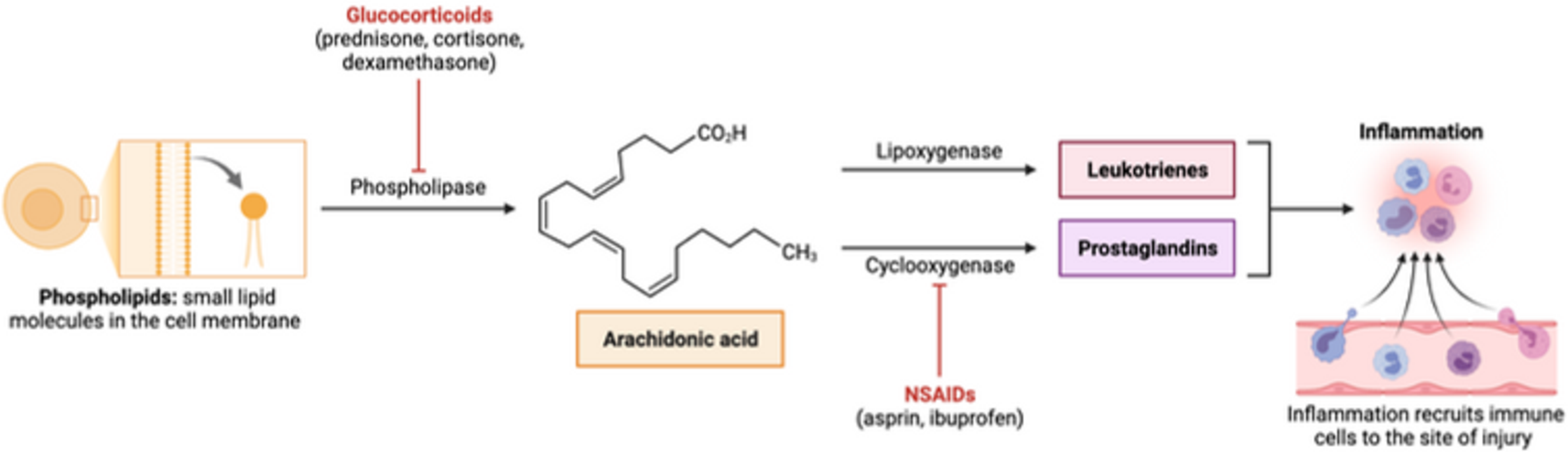
    Increased blood flow to inflamed area (vasodilation)
  - Swelling

    Accumulation of fluid (increased vascular permeability)
  - Pain

    Release of chemicals that stimulate nerve endings
  - Loss of Function*

INFLAMMATION

Arachadonic Acid Pathway



COX Pathway

Normally expressed

COX-1

↓

Prostaglandins

↓

Cytoprotective

Decrease acid production
Increased mucus production
Maintains renal blood flow
“House keeping PGs”

Induced by inflammatory mediators

COX-2

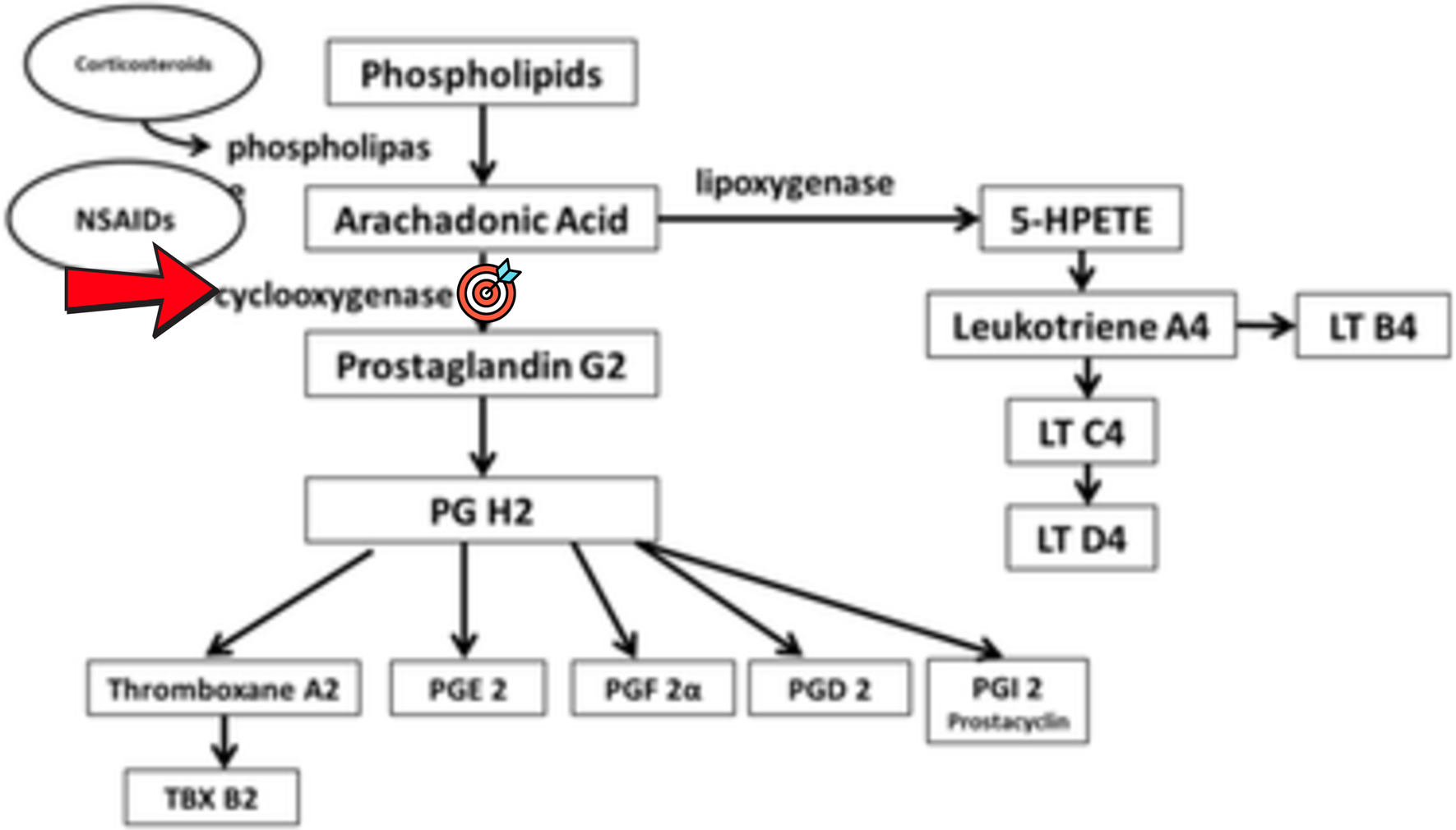
↓

Prostaglandins

↓

Pro-Inflammatory

Vasodilation, increased permeability, migration of inflammatory cells
“INDUCIBLE PGs”


Corticosteroids
Phospholipids
phospholipas
NSAIDs
Arachadonic Acid
lipoxygenase
5-HPETE
cyclooxygenase
Leukotriene A4
LT B4
Prostaglandin G2
LT C4
PG H2
LT D4
Thromboxane A2
PGE 2
PGF 2α
PGD 2
PGI 2
Prostacyclin
TBX B2

COX-1 VS COX-2

- **Theory behind COX-2 specific inhibitors (aka COX-1 sparing)**
  - Block the Bad
  - Leave the Good
  - No adverse effects

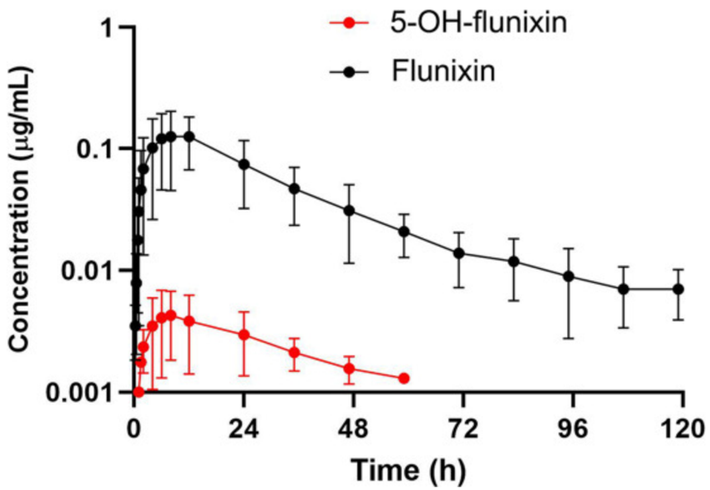
- **Not that simple! A lot of overlap**
  - **COX-2 constitutively expressed** in kidney
  - **COX-2** is needed for mucosal healing in GI tract

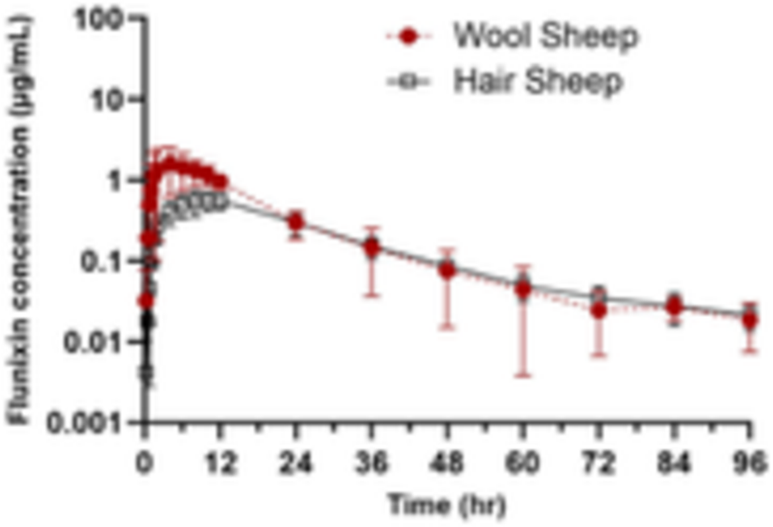
- Specificity of most drugs is overcome at high doses

CLINICAL USE OF NSAIDS

- **Analgesia**
  - Pain associated with inflammation → Very effective!
  - Pain independent of inflammation → Less effective
  - Best for mild-moderate pain; adjunctive to other therapy for severe pain
  - Tolerance and dependence **DO NOT** occur
- **Fever**
  - ALL NSAIDs reduce fever
  - May mask response to other therapies?
    - **Be judicious for this use**

- **Clinically Important PK Parameters – SPECIES DIFFERENCES**





Dr. Mzyk's Clinical Note

Cats are **NOT** Small Dogs
Goats are **NOT** Small Cows
Sheep are **NOT** Goats

Choosing an NSAID by Species (Food Animals)

- **Bovine- Recommended**
  - Flunixin meglumine - **Intravenous**
    - Labeled for pyrexia associated with BRDC and endotoxemia
    - Control of inflammation in endotoxemia
  - Flunixin meglumine - **Transdermal**
    - **First drug labeled for pain in a food animal species!**
      - Specifically, foot rot pain.

Choosing an NSAID by Species (Food Animals)

- **Bovine- Extra Label Drug Use**
  - ELDU permitted for analgesia
    - Meloxicam
    - Phenylbutazone - Prohibited in lactating dairy cattle
- **Swine**
  - Flunixin meglumine → Intramuscular injection
    - Pyrexia associated with swine respiratory disease
  - ELDU - meloxicam, Ketoprofen

Not the same as Banamine
(This is labeled for swine)

Choosing an NSAID by Species

- **Small Ruminant – Extra Label Drug Use**
  - No labeled products in US for SR species
  - ELDU permitted for analgesia

- **Meloxicam**
  - **Dose:** Typically 0.5 mg/kg – 1.0 mg/kg PO
  - **Clinical use:** disbudding, surgical pain, lameness
  - **Risks:** GI ulceration (long dosing duration), extended withdrawal intervals, not very effective for pyrexia

OTHER NSAIDS

- **Aspirin – Limited/No efficacy**
  - Does not have FDA approval in veterinary species
  - No studies showing any efficacy in pain control
  - Generally recognized as safe (GRAS)

- **Carprofen**
  - Provided analgesia after claw amputation in sheep
  - **High bioavailability** + **Prolonged duration** → Extended dosing intervals

OTHER NSAIDS

- **Firocoxib**
  - More COX-2 Selective
  - More studies needed but seems to show efficacy
  - High bioavailability + Prolonged duration → Extended dosing intervals (SID)

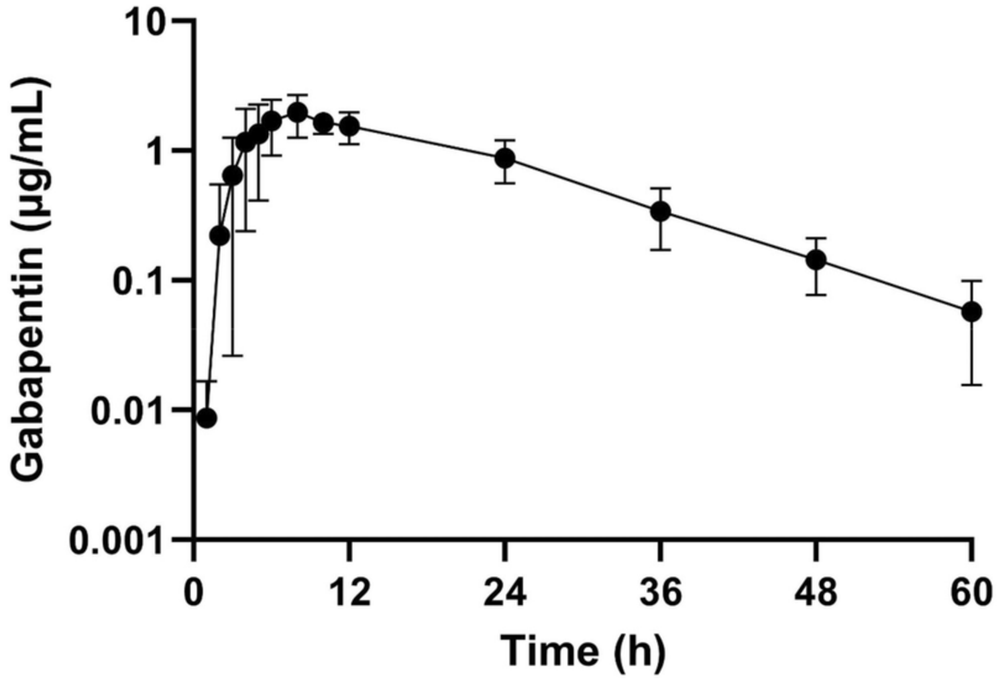
- **Ketoprofen**
  - Nonselective COX inhibitor
  - Approved for use as an analgesic drug for cattle in Canada

OPIOIDS

Morphine	Butorphanol	Fentanyl (?)
μ (mu) -agonist	**κ (kappa) agonist/partial mu-antagonist**	**μ (mu) -agonist (100x more potent than morphine)/Kappa antagonist**
Sheep/Goats: **0.05 - 0.2 mg/kg IV/IM/SC** Q4-8 hours **Cattle:** **0.1 – 0.5 mg/kg IV/IM/SC** Q4-8 hours (Generally start lower end of dosing range.	**Sheep/Goats/Cattle:** **0.05 - 0.2 mg/kg IV/IM/SC** Q4-8 hours ***Butorphanol can make calves vocalize!**	**Sheep/Goats/Cattle:** **2.5 ug/kg/hr transdermal patch** Q72-96 hours **Side effects:** Ileus, Depression, Pyrexia. Tachypnea, Ataxia

GABAPENTIN

- **Gabapentin**
  - 5-20 mg/kg PO (Generally start at 10 mg/kg)
    - q8-12 hours
  - **Mechanism:** Inhibits calcium channels
  - Clinical use: Potentiates NSAID analgesia
  - Considered ELDU in all food producing species



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LOCAL ANESTHESIA

- **Lidocaine** **Small ruminants are sensitive to lidocaine!**
  - **Mechanism:** Sodium channel blockers
- **Clinical use**: regional anesthesia
  - Beware of toxicity in small ruminants
    - **Toxic Dose: 5 mg/kg** → I generally dilute to 0.5-1% in saline

- **Signs of Toxicity:**
  - Muscular tremors, severe depression, hypotension, convulsions

NON-TRADITIONAL THERAPIES

- **Acupuncture – individual responses vary!**
  - Proposed therapeutic benefit:
    - Increased endogenous opioid formation
    - Increase microcirculation to site of injury (improved drug penetration?)
    - Faster nerve healing
  - VERY Challenging to study!

REGULATORY CONSIDERATIONS

AMDUCA: Animal Medicinal Use and Clarification Act - 1994

Permits veterinarians to prescribe extra label uses of certain approved new animal drugs and approved human drugs for animals under certain conditions.

REGULATORY CONSIDERATIONS

AMDUCA: Animal Medicinal Use and Clarification Act - 1994

Extra Label Drug Use includes:

- Different Species
- Different Route
- Different Dose
- Different Duration

Limitations with AMDUCA

- Lay person cannot give ELDU
- No ELDU in medicated feeds
- Cannot result in a residue
- Needs to use FDA approved drugs (human/veterinary products)

REGULATORY CONSIDERATIONS

- **KEY POINTS:**
  - **All drugs used need a withdrawal interval (WDI)**
  - **ELDU limited to therapeutic use (not production purpose)**
  - **WDI is required in all food producing species, even if they are a pet/companion animal**

QUESTIONS?

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