Nociception II

III. Mechanisms underlying the development of allodynia & hyperalgesia.

A. Peripheral Mechanisms: Results from the sensitization of nociceptors.

This is a cellular process responsible for the increased response of sensory neurons to noxious stimuli. It is thought to be due to the local release of a myriad of chemical mediators including bradykinin, histamine, serotonin, prostaglandins, cytokines and nerve growth factor (NGF), which activate receptors on primary afferent nociceptors leading to activation of intracellular second messengers --> changes sensitivity of ion channels--> making the nociceptors more sensitive to thermal, chemical or mechanical stimuli.

Inflammatory mediators (prostaglandins, NGF, ect)

↓

G-protein coupled receptors or tyrosine kinase receptors

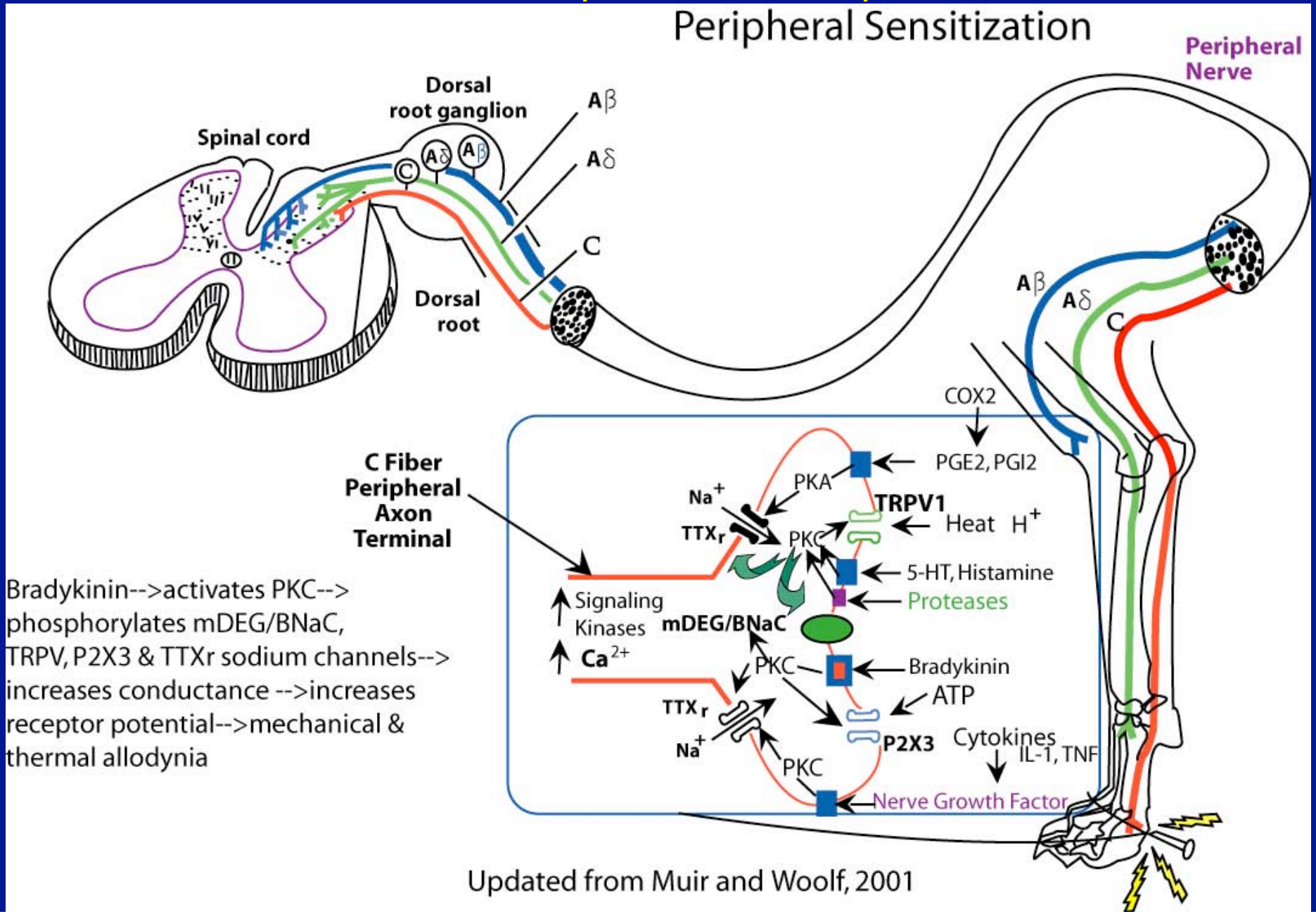
↓

Phosphorylate receptors and ion channels

↓

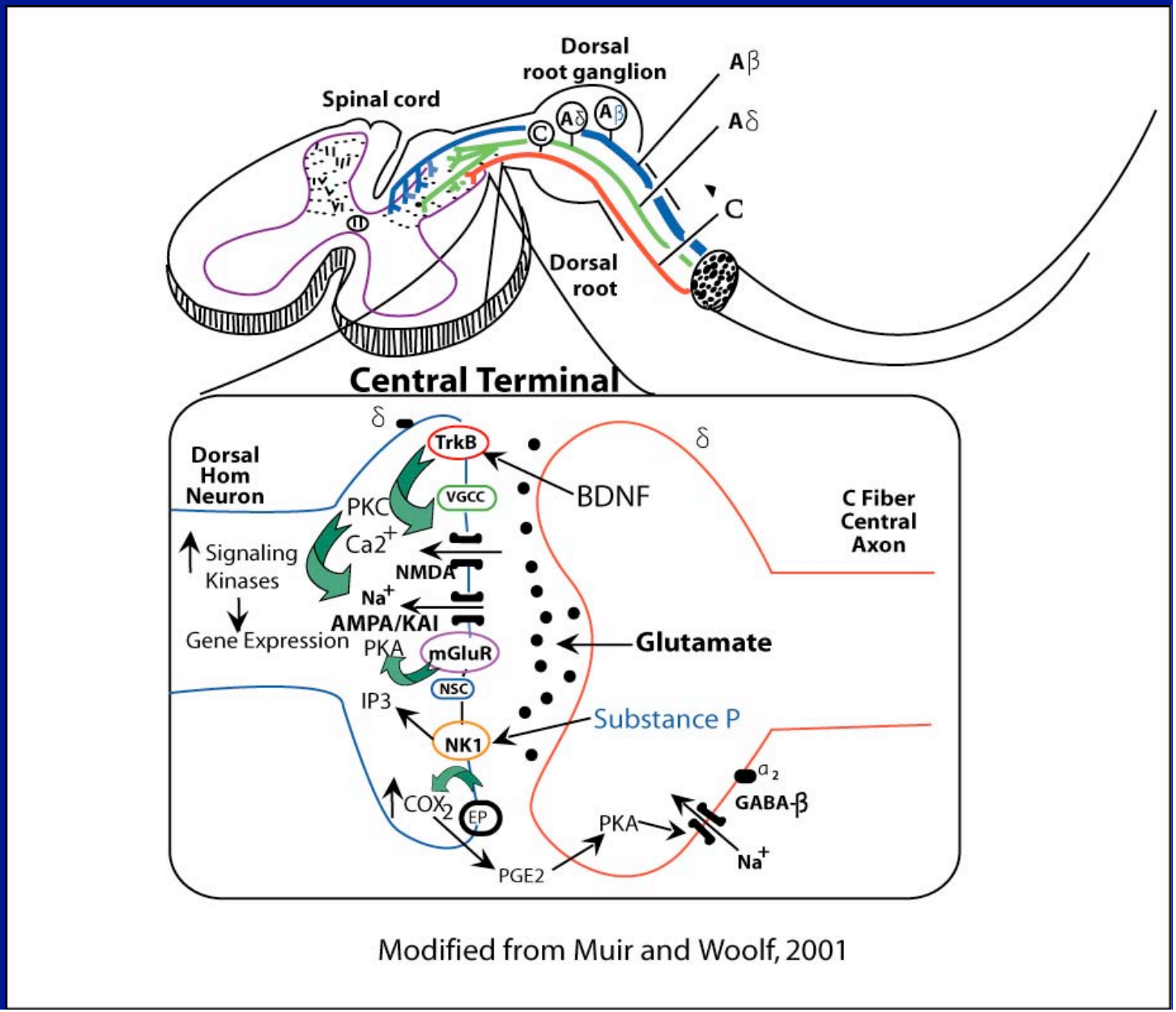
Changes in the threshold and kinetics of ion channels-->
Increases the sensitivity and excitability of nociceptors

Fig 1: Summary of peripheral mechanisms leading to peripheral sensitization. Mediators-->receptors on nociceptors-> ion conductance



Central Mechanisms: Spinal cord nociceptive neurons exhibit increased excitability following peripheral injury or inflammation.

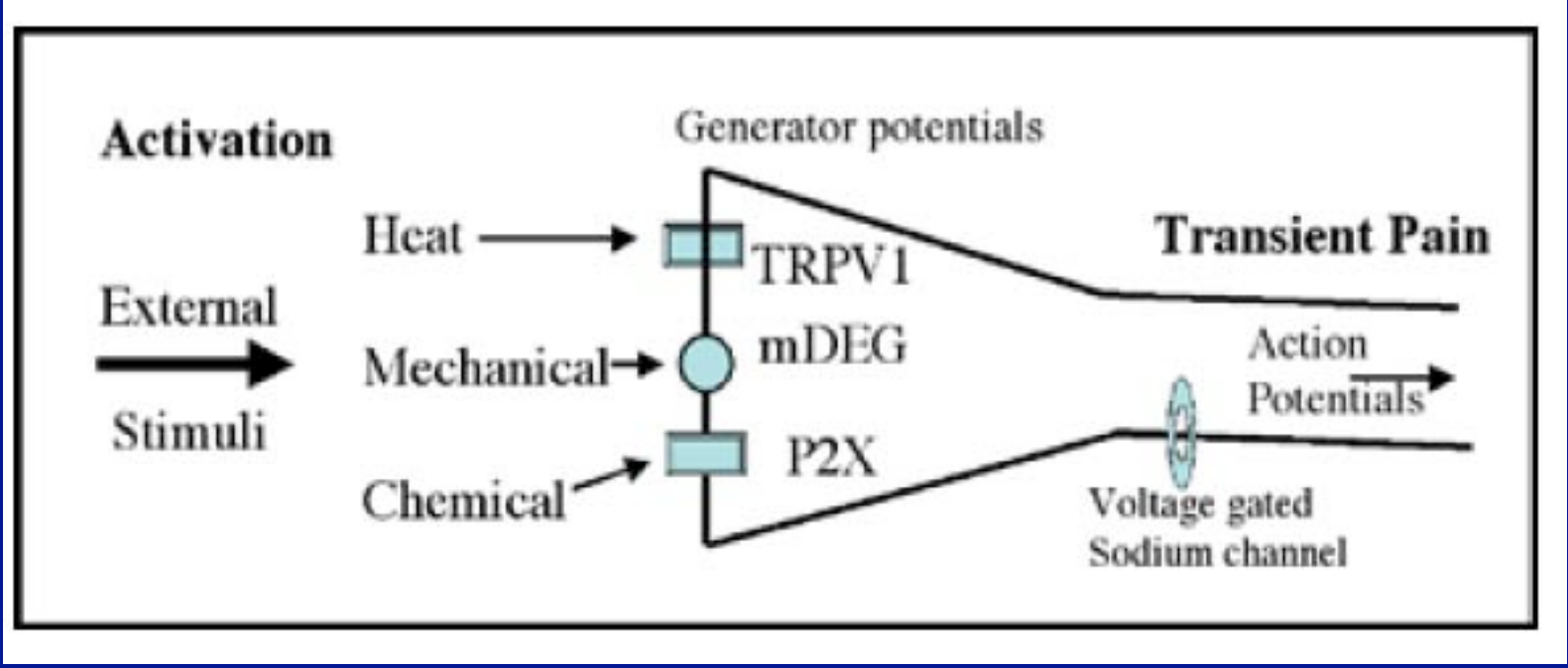
Increased release of glutamate, substance P and brain derived neurotrophic factor induce central sensitization by acting on membrane bound receptors--> ↑ Ca2+, PKA, PKC



Modified from Muir and Woolf, 2001

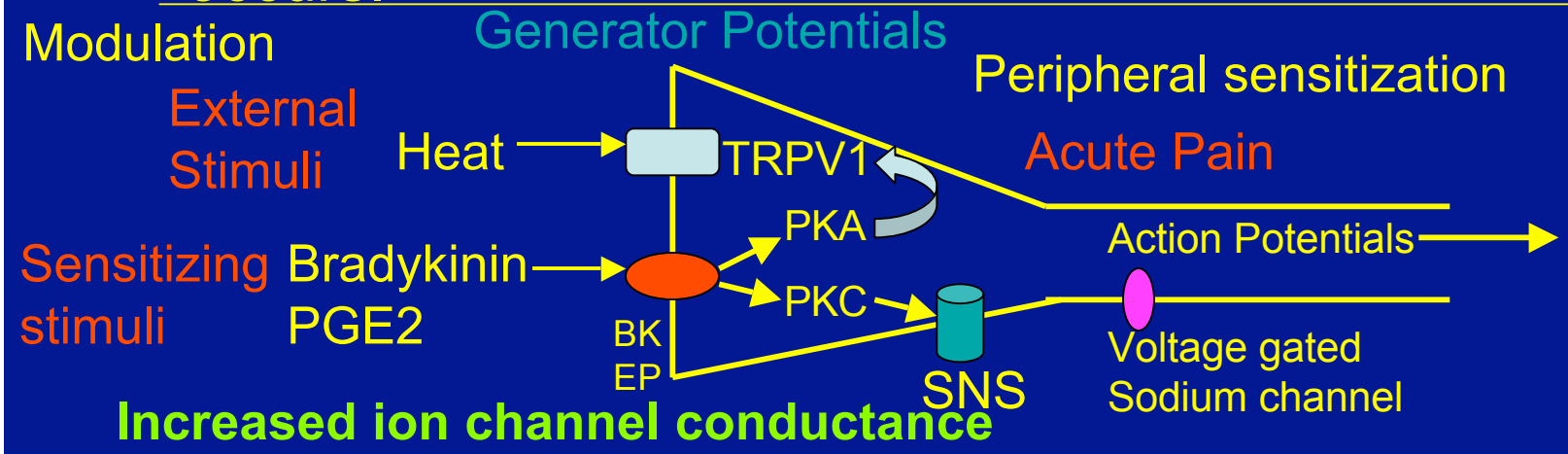
III. Types of Pain:

A. Transient (Physiological) Pain— elicited by activation of nociceptive transducers in skin or other tissues of the body in the absence of any tissue damage. It is evoked to protect animals or humans from physical damage by the environment or by excessive stress of the body tissues. It activates reflex withdrawal, arousal and autonomic responses.



Stimulus-→activates Nociceptive receptors→Depolarization→ Electrical signal To Spinal Cord

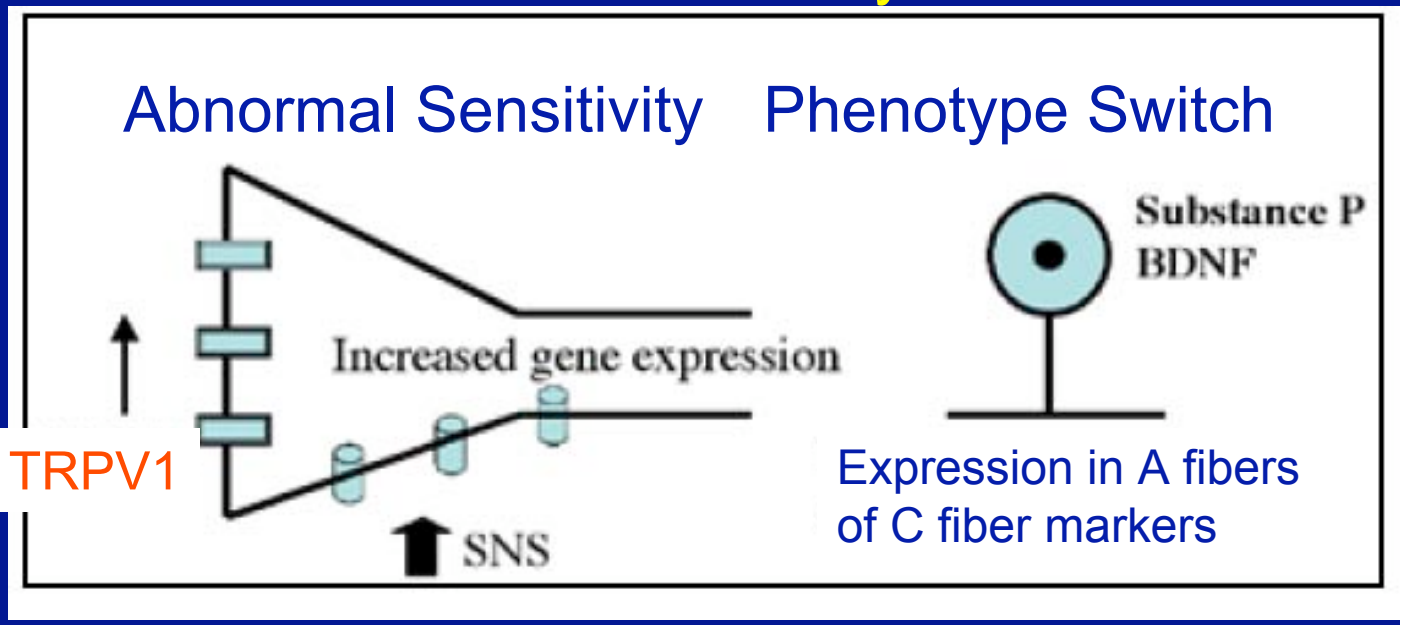
B. Acute Pain (Prolonged subchronic, e.g. surgical pain, inflammatory pain)—elicited by substantial injury of body tissue and activation of nociceptive transducers at the site of local tissue damage. The local injury alters the response characteristics of nociceptors, their central connections and the autonomic nervous system in the region. This type of pain is seen after trauma, surgical interventions and some diseases. Lasts a few days or weeks, but "healing" typically occurs.



Sensitizing agents (PGE2, 5-HT, Bradykinin)→increase the excitability of the nociceptive terminal→less depolarization needed to initiate an action potential

C. Persistent or Chronic Pain– (osteoarthritis, neuropathies, bac pain, cancer, etc.) are commonly triggered by an injury or disease, but may be perpetuated by factors other than the cause of the pain. Because chronic pain is unrelenting (lasting months or longer), it is likely that stress, environmental and affective factors may superimposed on the original damaged tissue and contribute to the intensity and resistence of the pain.

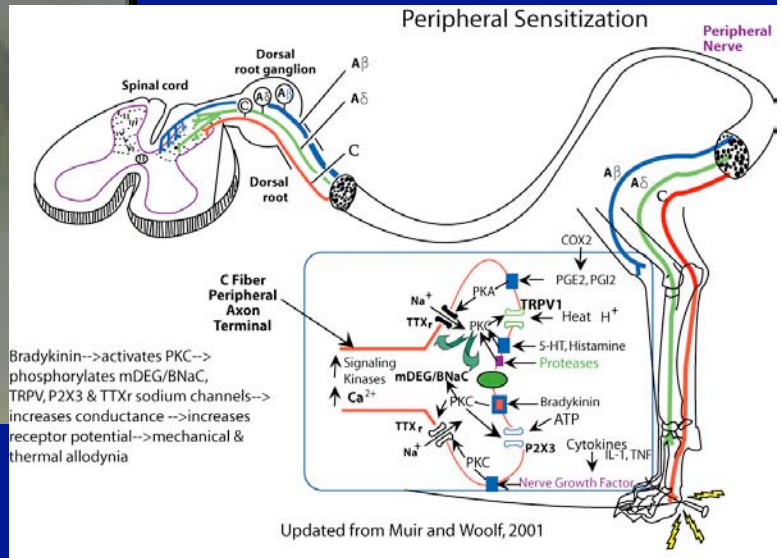
Abnormal sensitivity due to increased expression of TPRV1 & sensory neuron specific (SNS) sodium channels



Modification→altered gene expression

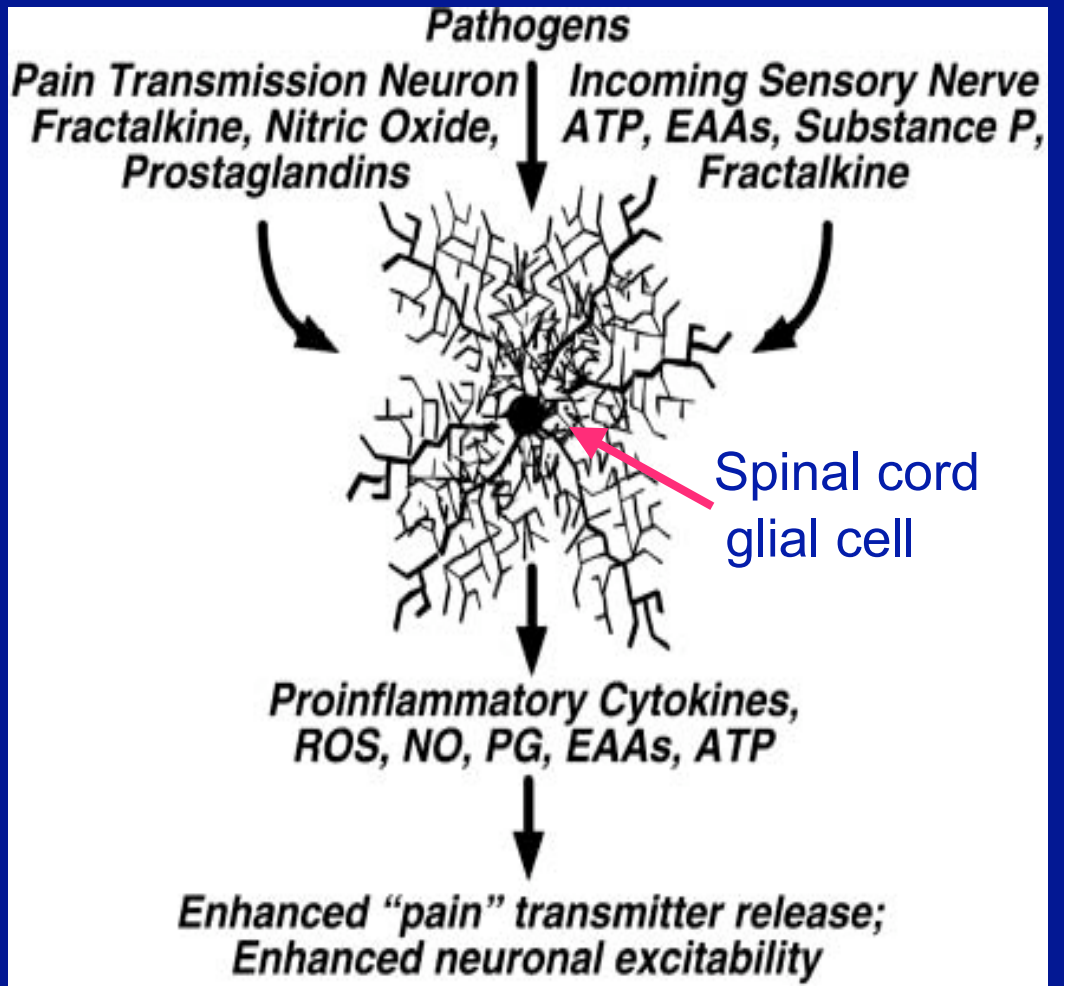
Transient receptor potential (TRP) channels are non-selective cation channels that respond to changes in temp.

*TRPV1- activated by noxious heat (≥43° C) & low pH (5.9)

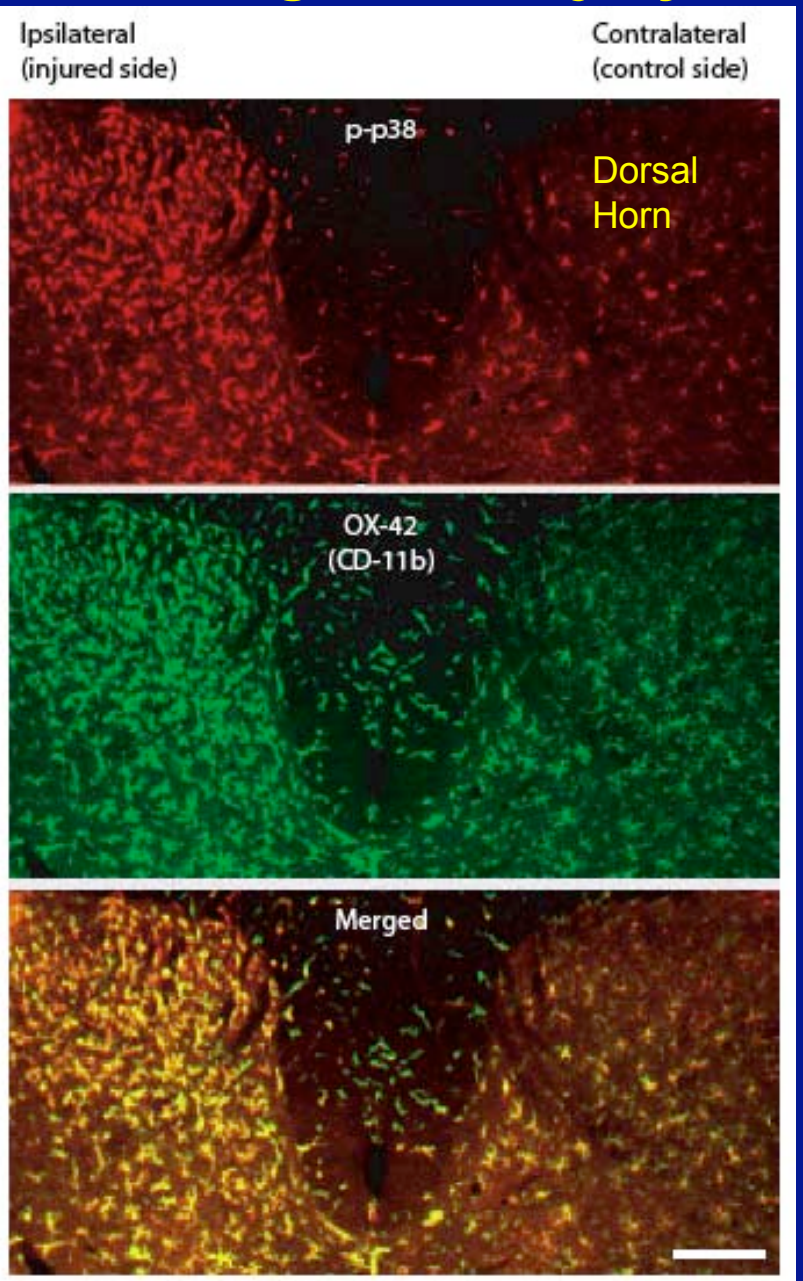


Note: The central (CNS) and peripheral (PNS) nervous systems are dynamic, not static, and are modulated by tissue damage and injury. In the spinal cord, immune-like glial cells (**astrocytes and microglia**) are activated in response to subcutaneous inflammation, nerve trauma and tumors. These glia are involve in the creation and maintenance of pathological pain states in part by releasing **proinflammatory cytokines** (TNF, IL-1, ect.)

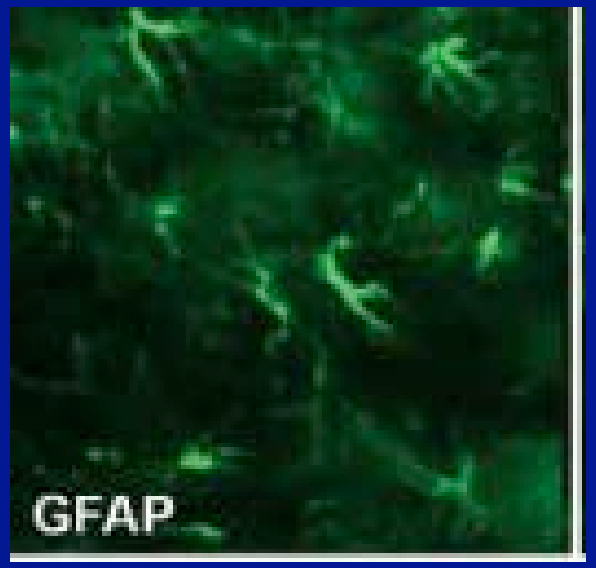
Glia act as a "volume control" for pain-they are not involved in normal everyday pain, but are critically involved in pain enhancement in chronic pain

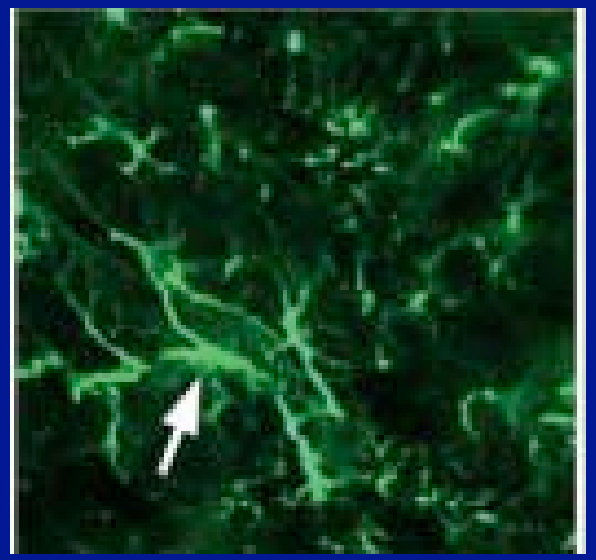


Increase in microglia following nerve injury

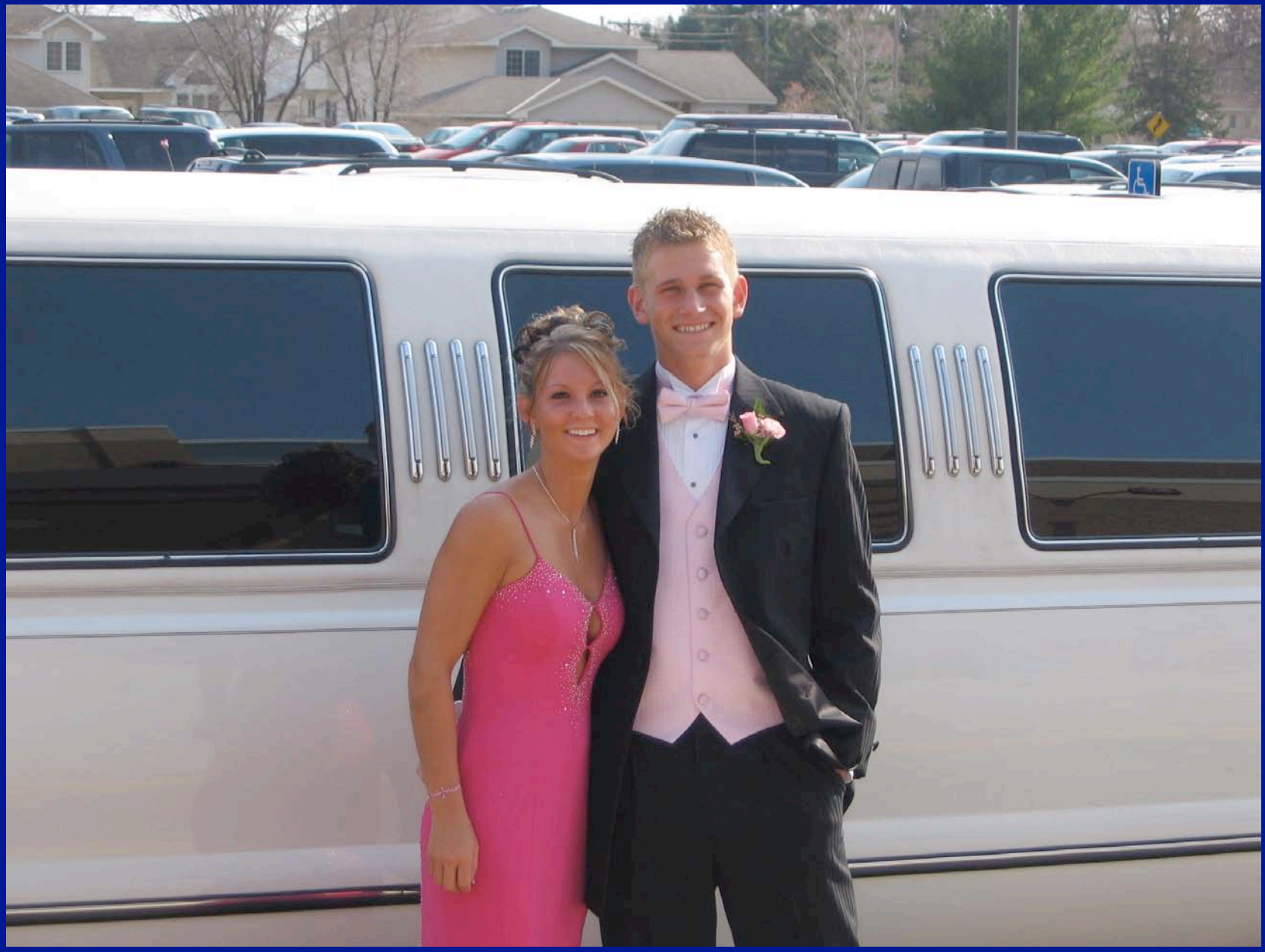


Increase in Astrocyte numbers In dorsal horn of animal with cancer pain





And now for something completely different!



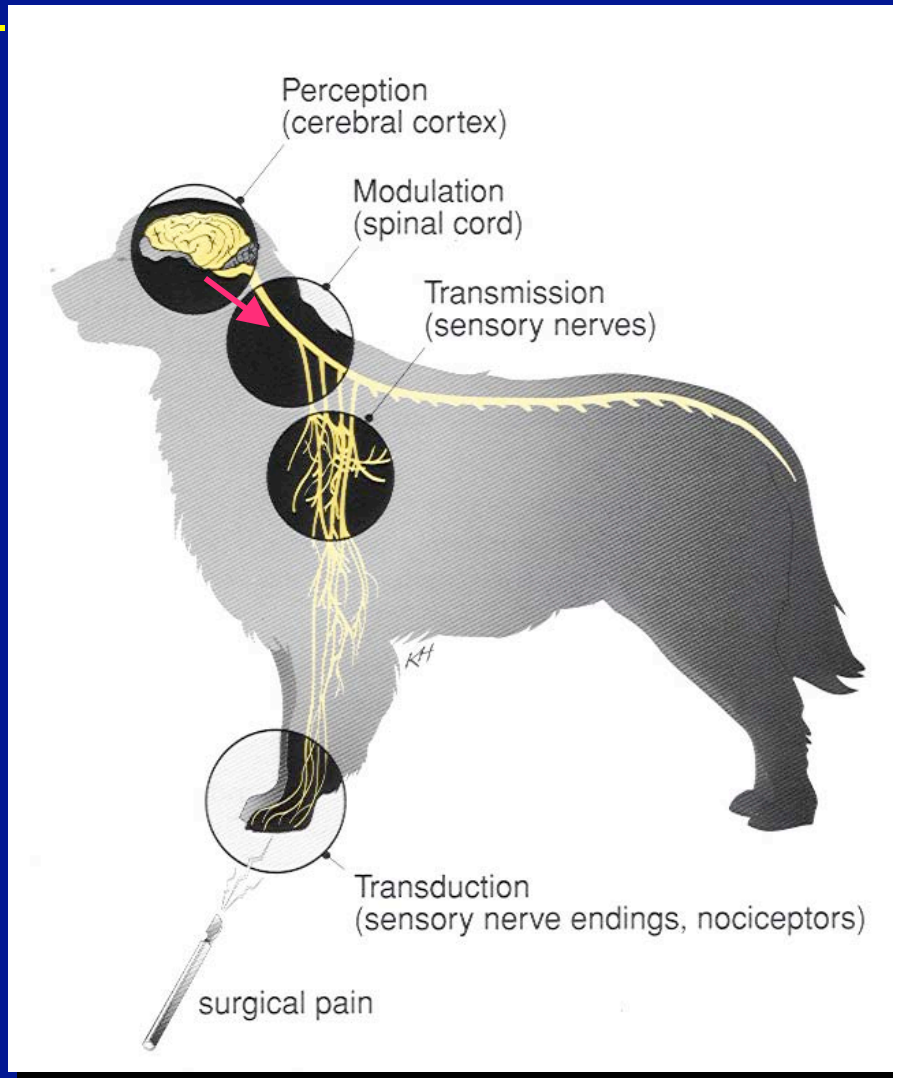

Xtreme
783-5657

The Endogenous Analgesia (Pain Suppression) System

Since the pioneering studies of Magoun and colleagues, it was known that the brain stem can exert a strong control over the spinal cord. Reynolds -->1969 -->potent analgesia by electrical stimulation of the midbrain in freely moving animals.

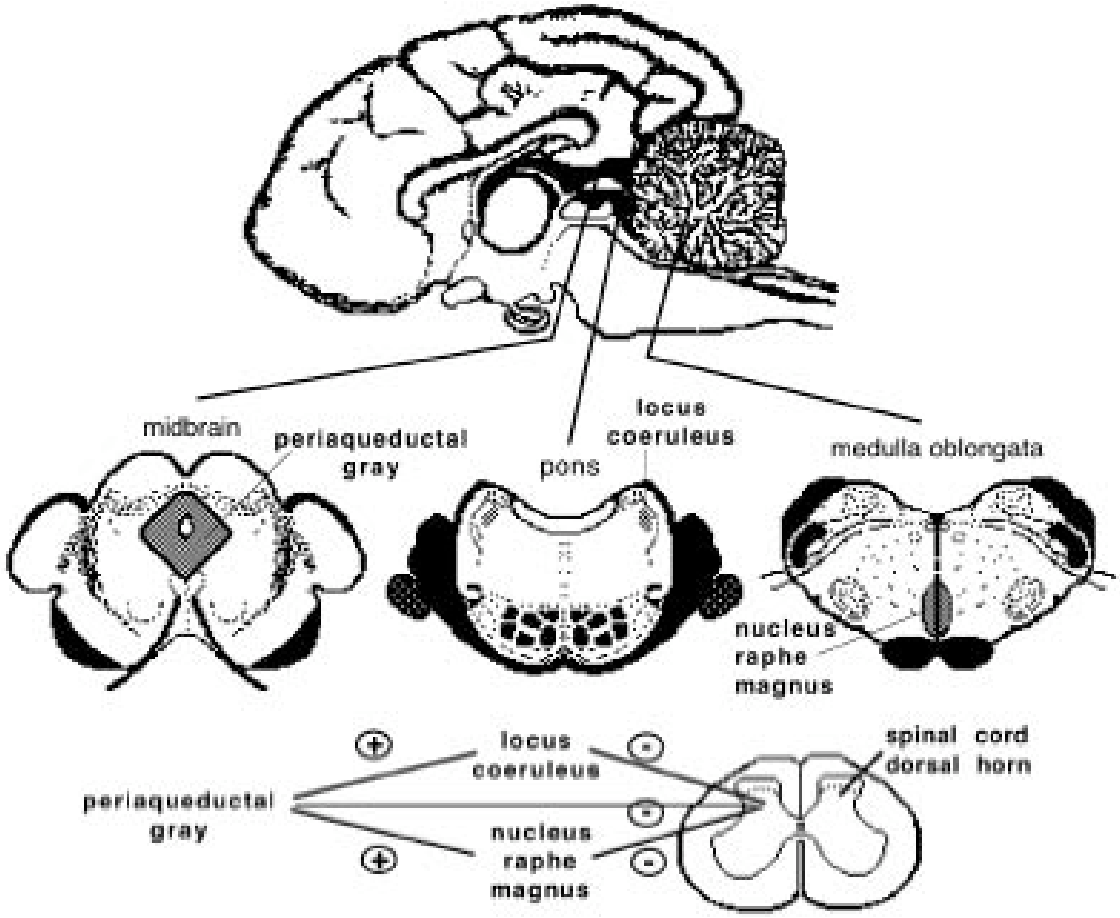
- **Modulation**
  - –Amplification or suppression of nerve signals in the spinal cord

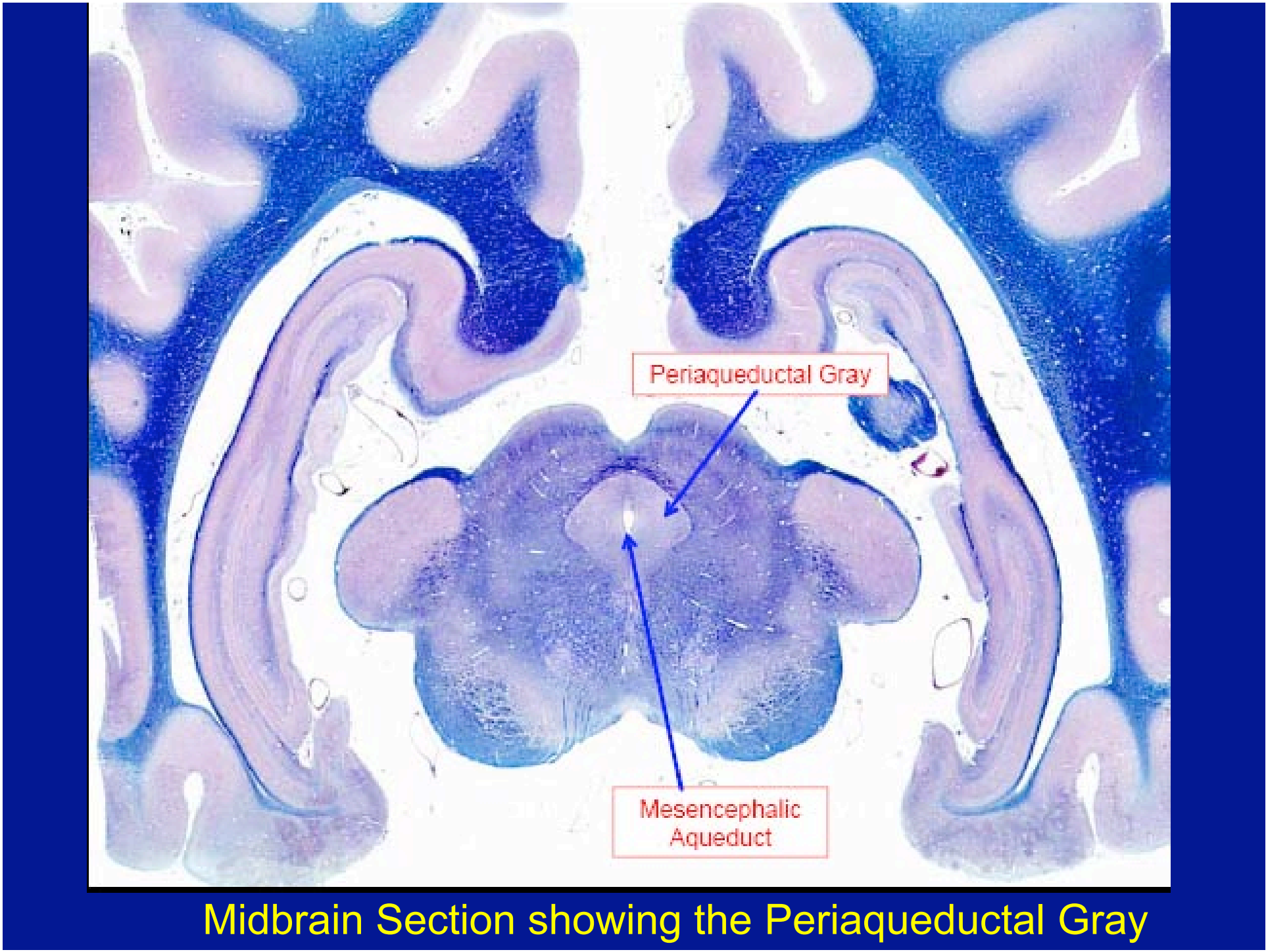
Narcotic drugs (e.g. morphine), acupuncture, hypnosis and electrical stimulation of selected brain regions -->activate endogenous analgesia system --->reduction in pain sensation.



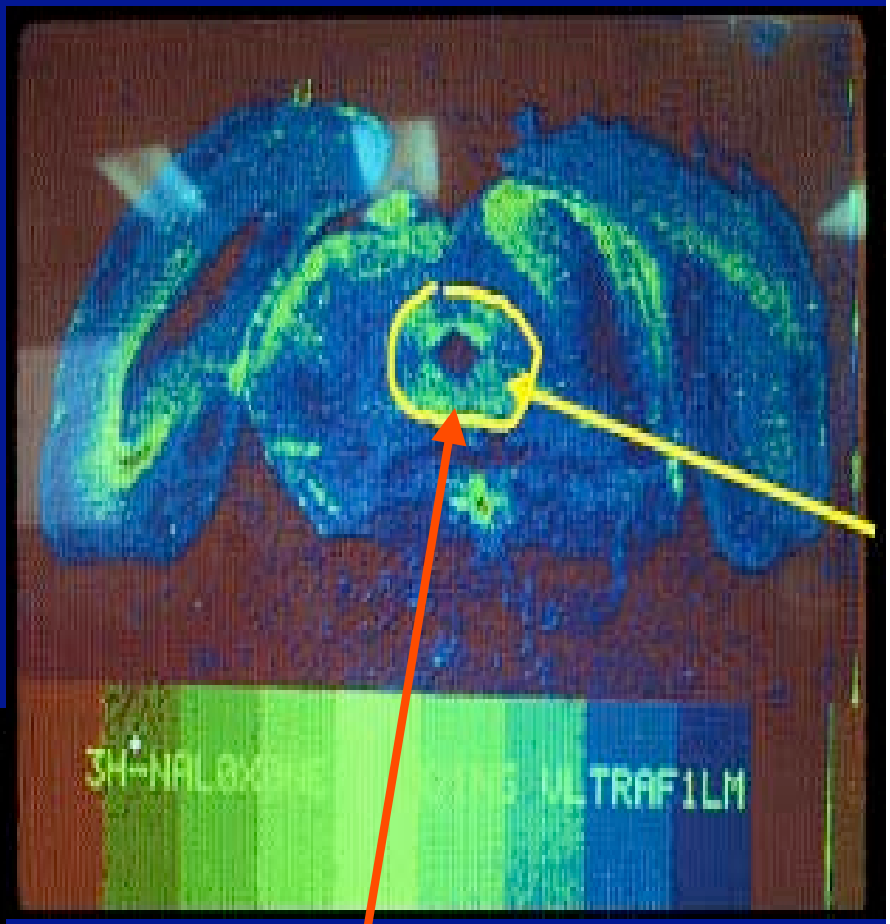
Components:

1. **Midbrain Periaqueductal Gray (PAG):** the region surrounding the mesencephalic aqueduct. It contains a high density of opiate receptors and has direct connections with the spinal cord and the nucleus raphe magnus. Opiate drugs, acupuncture or direct stimulation-->activates a descending pathway that excites neurons in the raphe magnus and locus coeruleus to inhibit spinothalamic and spinocervicothalamic neurons in the spinal cord.





Midbrain Section showing the Periaqueductal Gray



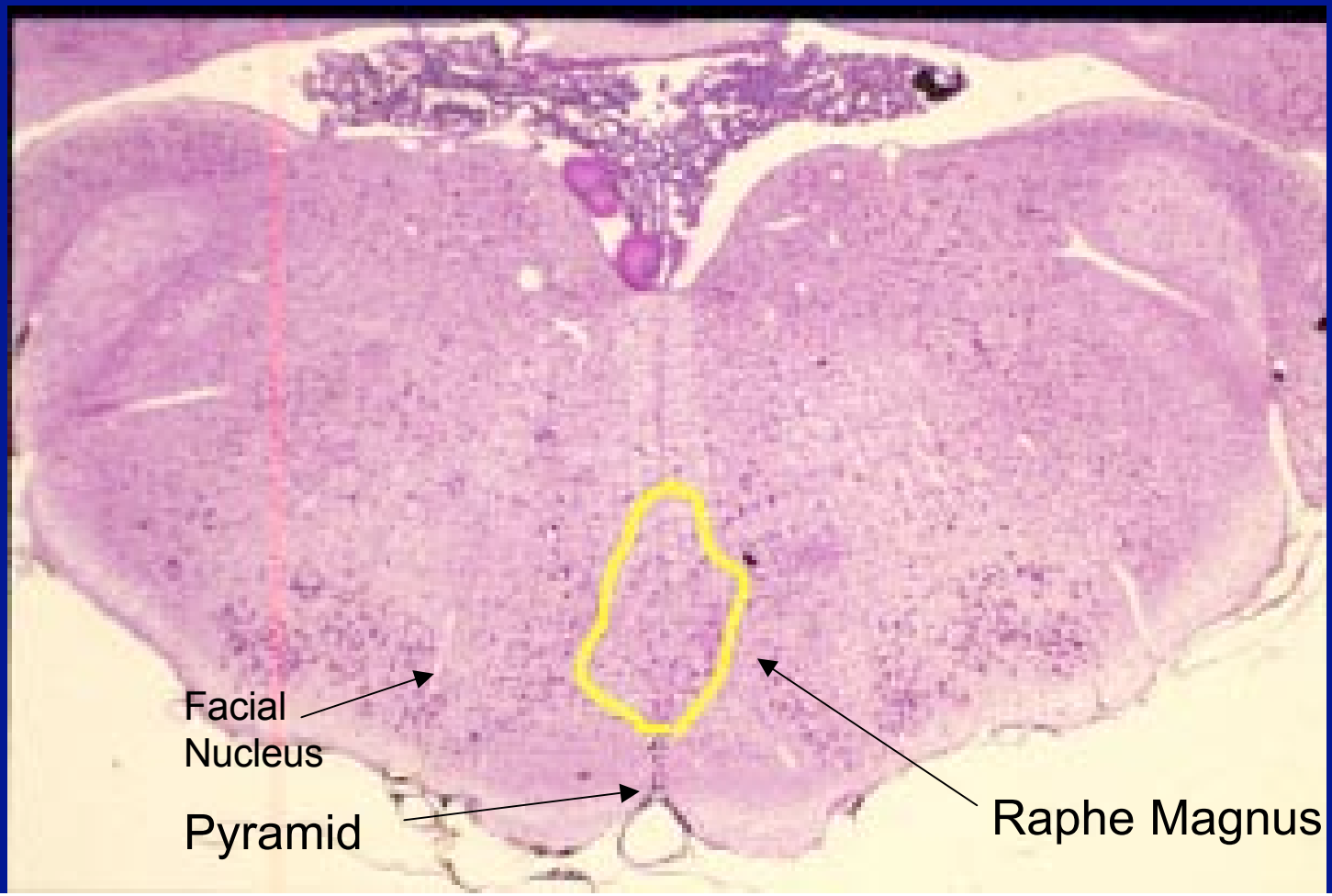
Opioid Receptor Distribution
In the Periaqueductal Gray

Sites in the cat midbrain where stimulation produces analgesia

2. Nucleus Raphe Magnus: located in the rostral medulla.

--Has high levels of serotonin

--Sends axons to spinal cord where they synapse in marginal nucleus and nucleus proprius to inhibit incoming pain signals

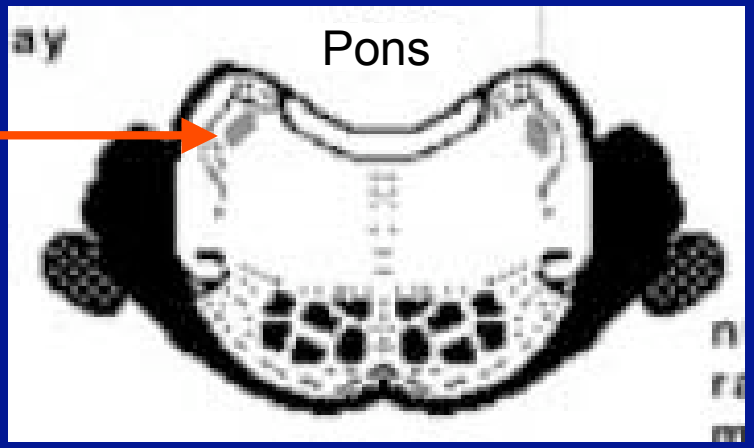


3. Nucleus Locus Coeruleus: located in the caudal pons near the floor of the fourth ventricle.

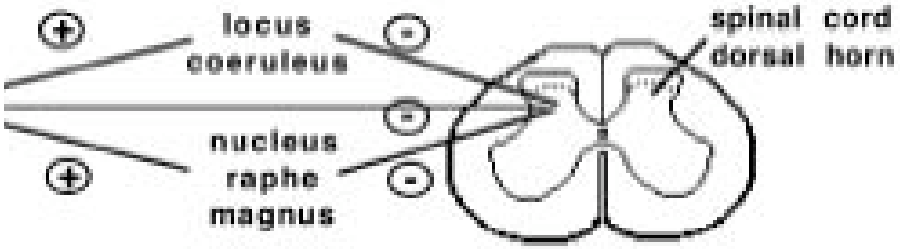
---Contains high levels of norepinephrine

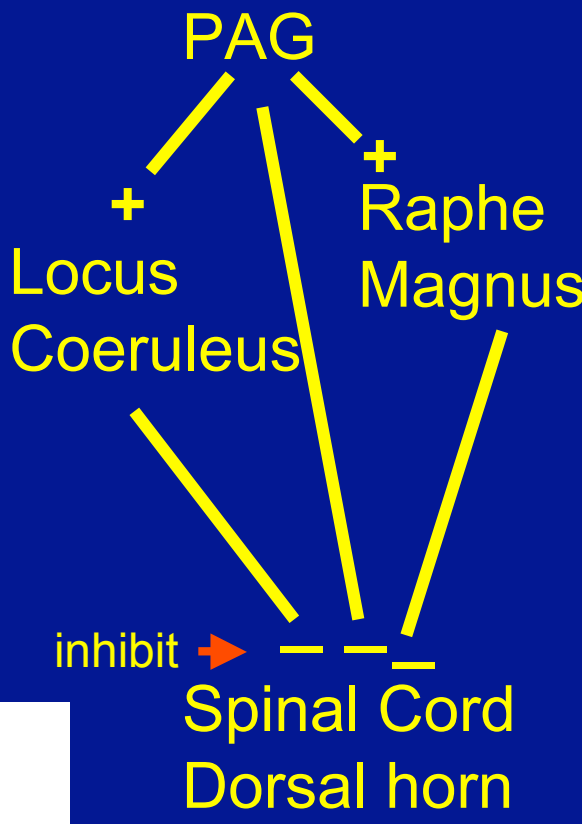
---Axons from locus coeruleus descend to spinal cord -->inhibit neurons in the marginal nucleus & nucleus proprius--> inhibits pain transmission

Locus Coeruleus



Periaqueductal gray





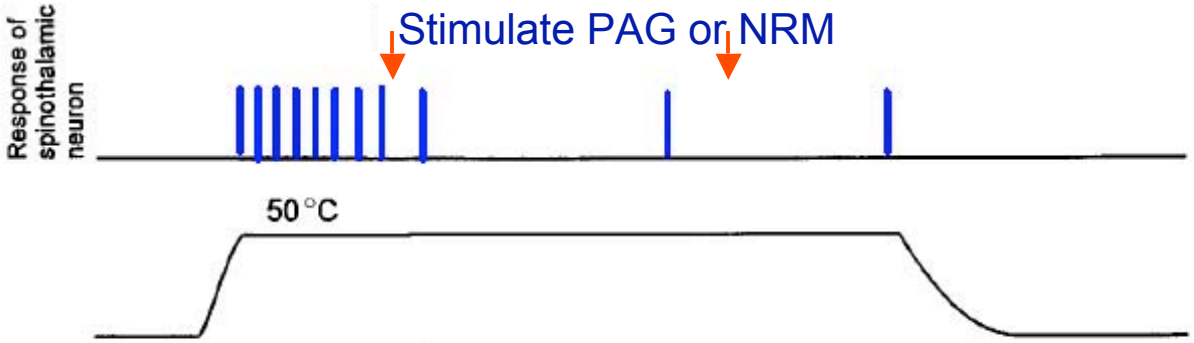
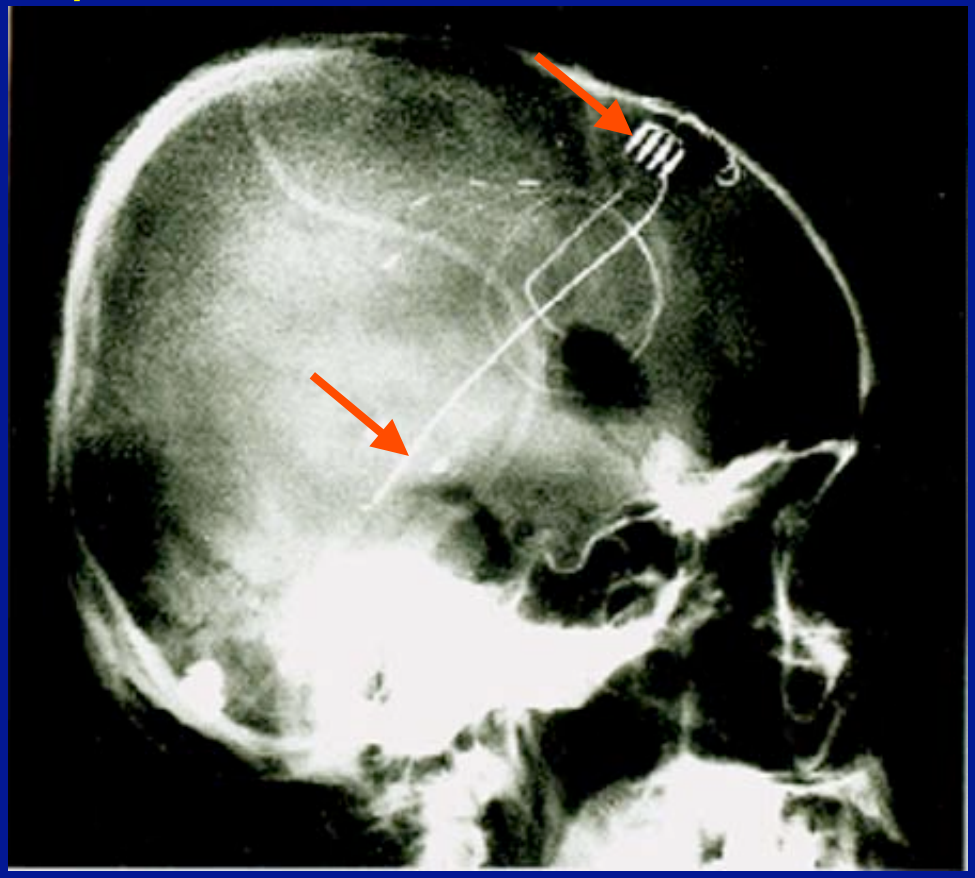


Figure 6: Electrophysiological effects of activation of neurons in the PAG and raphe magnus.

Radiograph illustrating a stimulating electrode in the human periaqueductal gray of a terminal cancer patient. The patient can self-stimulate to produce pain relief.



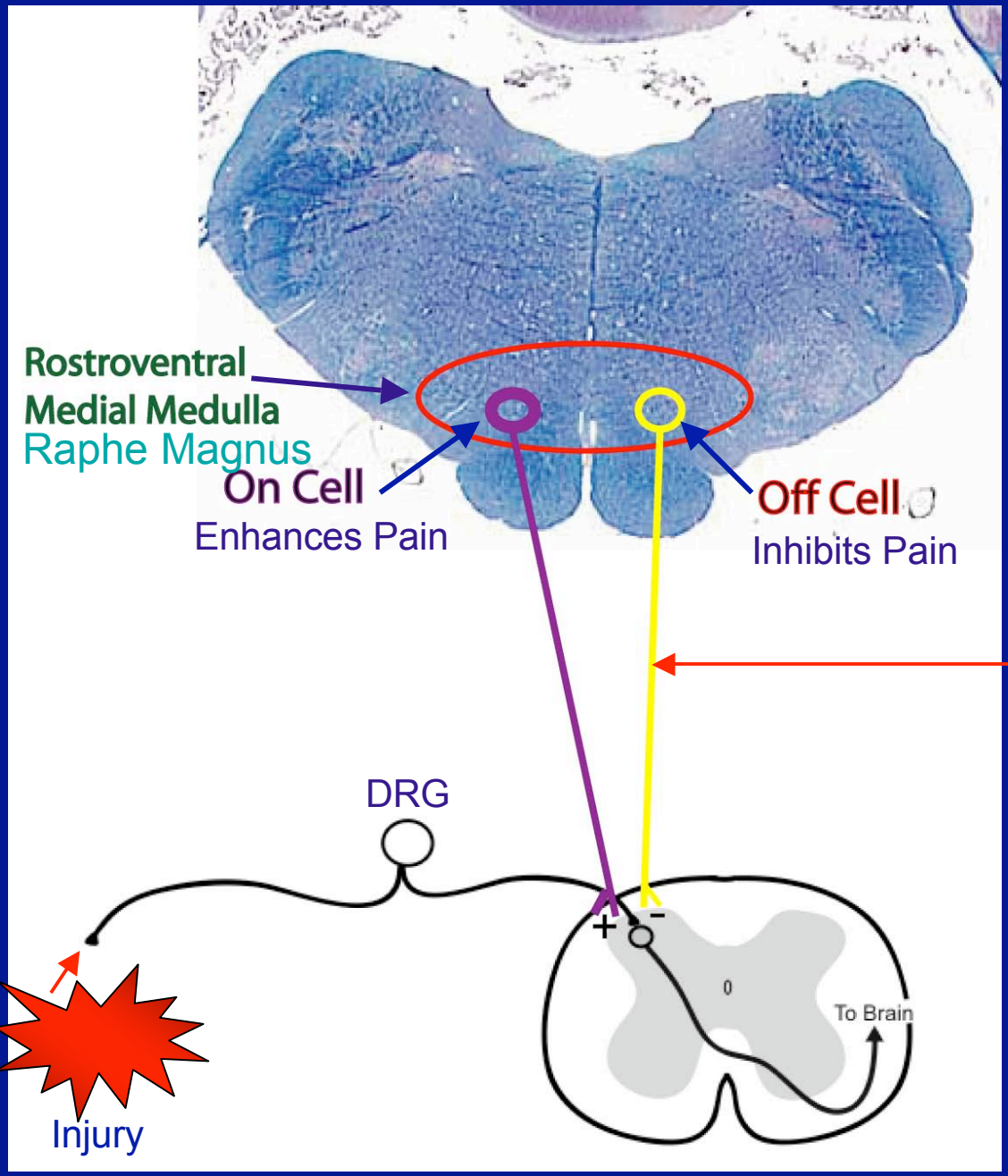
Note: Females have a separate descending inhibitory system that is estrogen sensitive

Endogenous Pain Activation System:

There also appears to be an endogenous pain activation system that actually enhances pain. This pain enhancement system appears to help maintain chronic pain status. This system is also centered in the brainstem. The PAG and raphe magnus have collections of two physiologically different types of neurons that appear to be related, one the one hand, to pain enhancement and, on the other hand, to pain suppression.

Endogenous Pain Activation System:

There also appears to be an endogenous pain activation system that actually enhances pain. This system maintains chronic pain states.



Pain Assessment in Animals

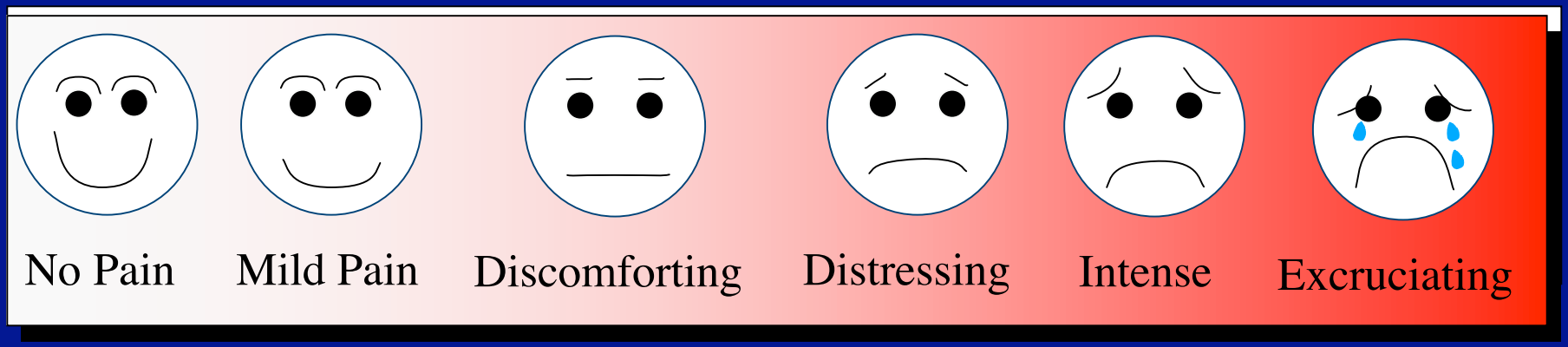
Pain assessment is considered part of every patient evaluation regardless of the presenting complaint

Animals & human infants can't tell you in words or phrases, ***you have to learn to recognize the signs:*** facial expressions, abnormal postures or gait, avoidance of activities, overt expressions, and symptomatic signs of pain, distress and suffering.

Pain Assessment in Animals

*You should recognize the importance of pain assessment as part of daily patient evaluation; obtain a pain score as a fourth vital sign (Temperature, Pulse, Respiratory rate, Pain).

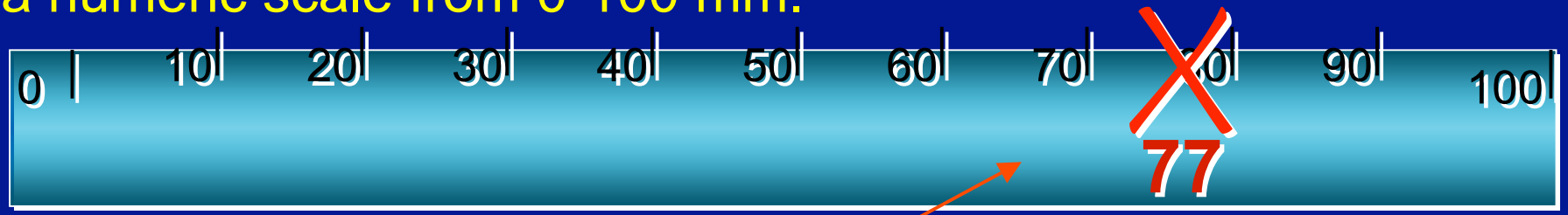
•In addition to behavioral assessment, you should also utilize a
•scoring system for pain. You can use a visual analog scale (VAS)
• to evaluate pain (as well as successful pain management).



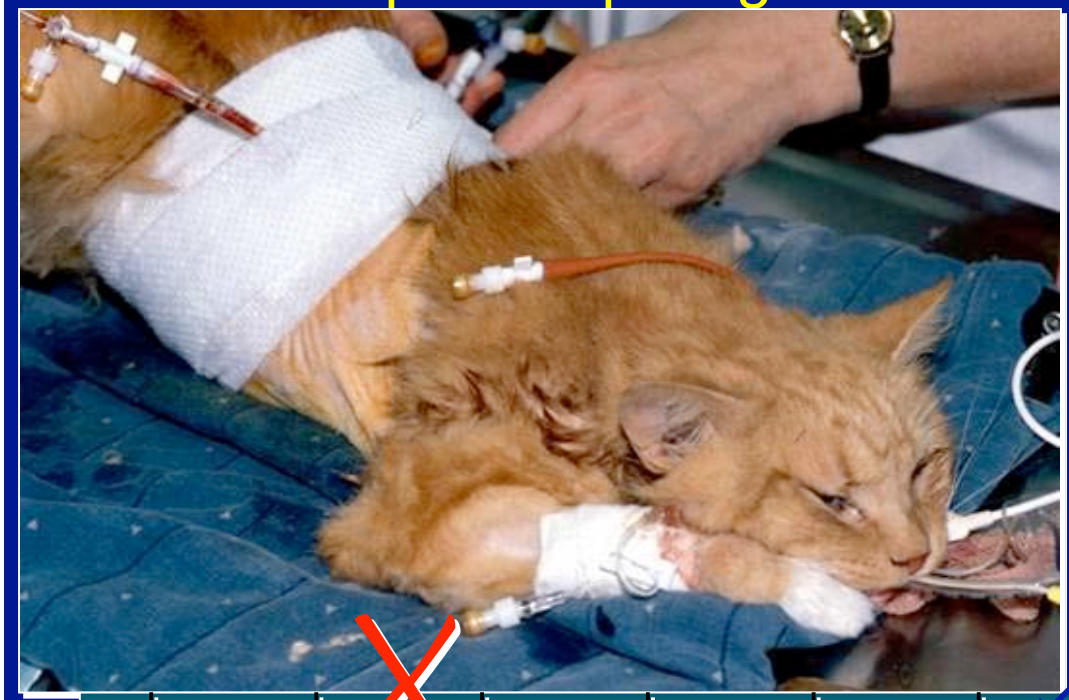
(Scale as Used in Human Pain Scoring)

Pain Scales: Visual Analog Scale (VAS)

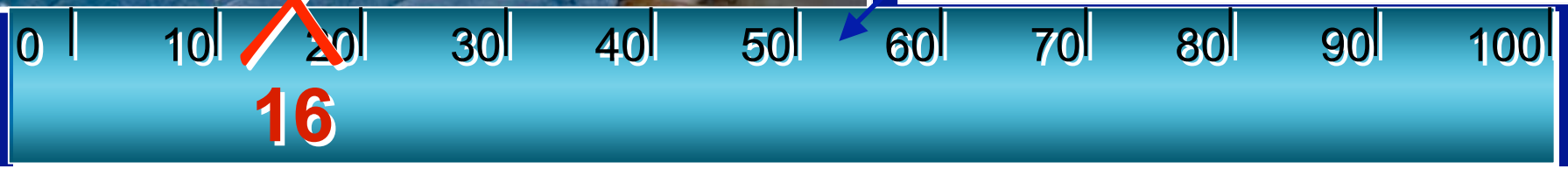
- A VAS scale goes from “no pain” to “worst ever pain”, based on a numeric scale from 0-100 mm.



Animal with pain requiring treatment



Evaluation after treatment



Pain Scales: Visual Analog Scale

Behavioral categories used to assess VAS Pain Score in Dogs

1. Demeanor:
   - Anxious
   - Depressed
   - Distressed
   - Quiet

2. Response to People:
   - Aggressive
   - Fearful
   - Indifferent
   - Sullen

3. Response to Food:
   - Disinterested
   - Eating hungrily
   - Picking
   - Rejecting food

4. Posture:
   - Curled
   - Hunched
   - Rigid
   - Tense

5. Mobility:
   - Lame
   - Slow/ reluctant
   - Stiff
   - Unwilling to rise

6. Activity:
   - Restless
   - Sit/ lie still
   - Sleeping

7. Response to Touch:
   - Crying
   - Flinching
   - Growling
   - Guarding
   - Snapping

8. Attention to Painful Area:
   - Biting
   - Chewing
   - Licking
   - Looking
   - Rubbing

9. Vocalization:
   - Crying
   - Groaning
   - Howling
   - Screaming
   - Whimpering

10. Physiological signs:
    - Tachycardia
    - Panting
    - Tachypnea
    - Pyrexia

Pain assessment using a standardized scale or scoring system should be recorded in the medical record for every patient evaluation

Pain Relief in Animals

Classes of Pain Medications

Local anesthetics [Carbocaine, lidocaine, bupivacaine]- nerve blocks

Corticosteroids [Prednisone]

Non-steroid anti-inflammatory drugs [Apirin, Rimadyl (carprofen injectable), deracoxib oral, tepoxalin oral]

Alpha$_2$ agonists [xylazine, detomidine, medetomidine]

Opioids [Buprenex Injectable (buprenorphine hydrocloride)]

Pain Relief in Animals: *Animals have pain = Treat it!*

Treatment related to Severity of Animal Pain

Mild
- NSAID's
- Steroids
- Local anesthetics
- Physical therapy

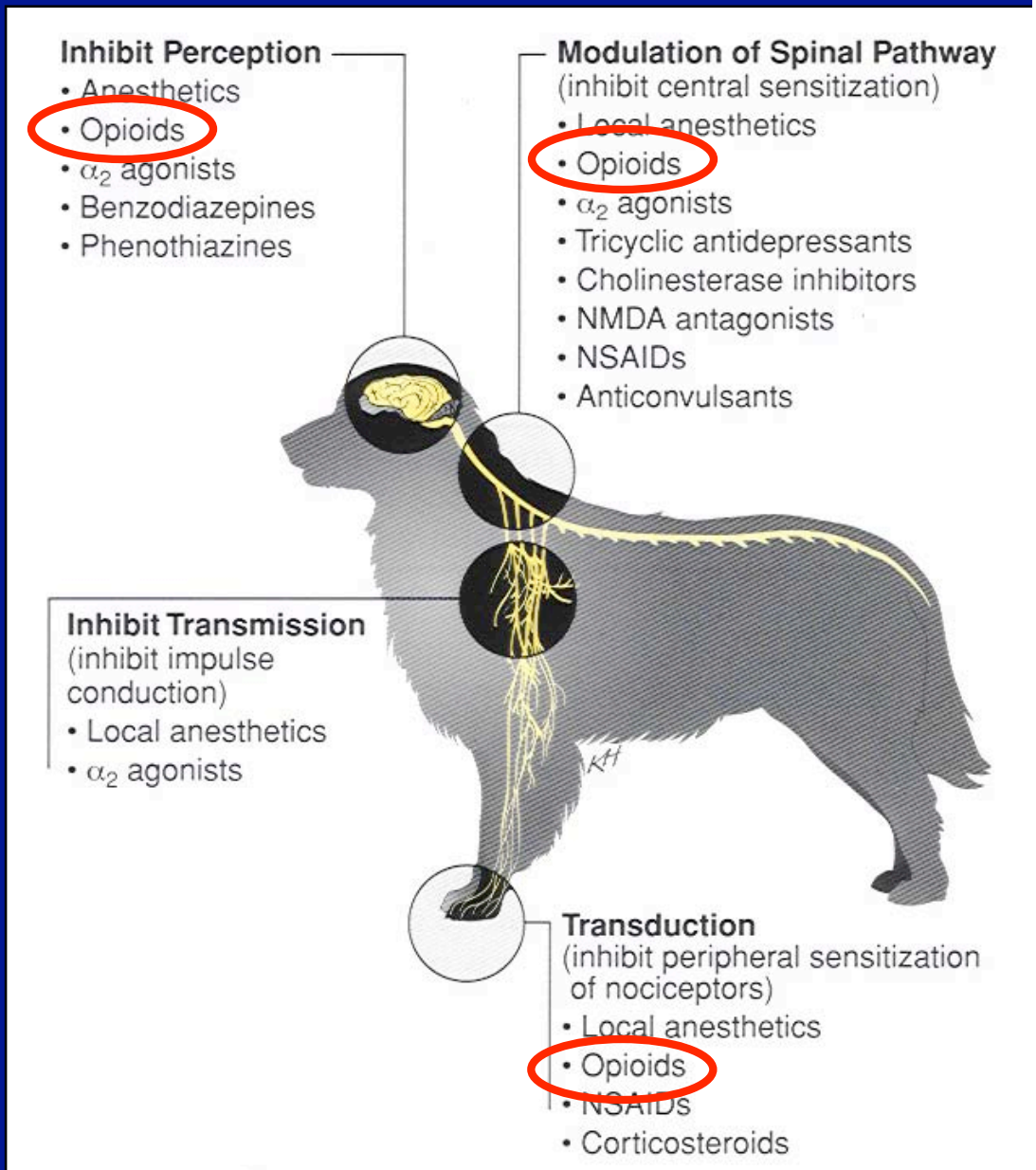
Moderate
- Opioid agonists
- Opioid agonists/ antagonists
- $Alpha_2$ agonists

Severe: treatable
- Potent opioids with/without concurrent medications
- Permanent nerve blocks
  - neurectomies
  - implantable opioid pump

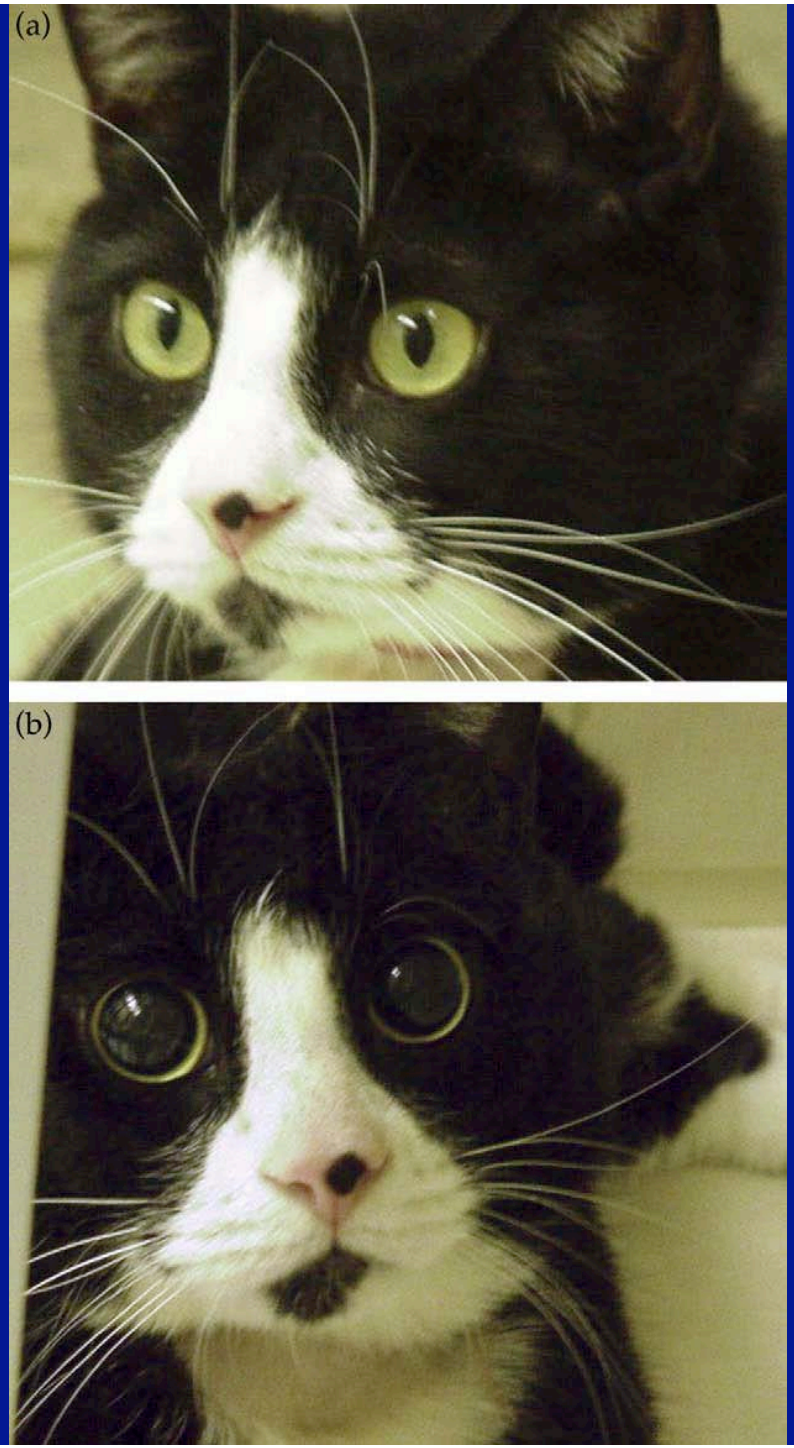
Severe: uncontrollable
- Euthanasia

Opioids

- **Decrease pain perception, anxiety, and distress**
- **Most effective when given before pain onset**
- **Rapid onset, long duration**
  - **Rapid onset with IV administration**
  - **Long duration with IM administration**



Oral buprenorphine 3X daily provided excellent pain relief for this cat with a fractured jaw and pelvis.



Opiates cause mydriasis (pupillary dilation). Cat before (a) and after (b) administration of hydromorphone

A fentanyl transdermal patch provides persistent pain relief for several days without regular injections.

Good pain management results in a comfortable cat that will eat, drink and relax even while recovering from severe trauma

2. Acupuncture: The effects of acupuncture on the central and peripheral nervous system include activation of the body's endogenous pain modulatory systems, causing a release of norepinephrine, opioid substances and other neurotransmitters thereby altering nociceptive processing and perception.
[For additional information see the review by Mittleman and Gaynor JAVMA 217:1201, 2000]

American Academy of Veterinary Medical Acupuncture (AAVMA)

Courses in veterinary medical acupuncture are offered at the Colorado State University College of Veterinary Medicine

The Top 9 Signs You've Already Grown Up:

1. You keep more food than beer in the fridge
2. You go from 130 days of vacation time to 7
3. Jeans and a sweater no longer qualify as "dressed up"
4. MTV news is no longer your primary source of information
5. Over 90% of your time is spent at a computer for real work
6. You don't drink at home to save money before going to the bar
7. 6:00 AM is when you get up, not when you go to sleep
8. You hear your favorite song on an elevator
9. You go to the drugstore for ibuprofen and antacids, not condoms and pregnancy test kits