Mechanisms and Clinical Presentation of Pain
(MSNBIO 2622)

Descending Modulation of Pain

- Introduction and background
- Stimulation-produced analgesia (SPA)
- Character of descending systems
- Anatomy of descending systems
- Pharmacology of descending systems
- Functional significance of descending systems

Descending Modulation of Pain

- Sherrington – spinal transX → exaggerated reflexes →
tonic descending inhibition (from brainstem)

- Lundberg (1950s/60s) - descending inhibition of Flexor Reflex Afferents

- Reynolds (1969) – “Surgery in the rat during electrical analgesia induced by focal brain stimulation.” PAG, SPA. Raised possibility of the existence of an endogenous pain modulatory system, the importance of which was not appreciated until Liebeskind and trainees followed up in a 1971 Science paper

SPA (abdominal surgery):

- produced by stimulation at ventrolateral edge of PAG
- lasted up to 5 min after end of stimulation
- interpreted as analgesia (not paralysis) because rats could move during stimulation and responded to movements in the visual field and loud noises
• Yaksh - intra-PAG opioids → antinociception in primates and rodents

sites of morphine injections into the primate PAG and adjacent areas:
- >50%

• Liebeskind & Besson – inhibition of spinal nociceptive transmission from sites outside the PAG, not all of which produce behavioral antinociception (Willis – "inhibition is cheap")
• Ruda – no/few spinopetal afferents from the PAG to the spinal cord
• Proudfit – NRM lesions block opioid antinociception
• Basbaum and Fields – NRM

• focus initially only on inhibition
• because NRM is a 5-HT containing nucleus, and there's a long history of 5-HT and pain, descending inhibition was asserted to be serotonergic, which is supported by a report that
• PAG stimulation releases 5-HT in spinal cord (Yaksh)
• but, nothing is ever simple
neither PAG nor NRM stimulation-produced effects are fully blocked by intrathecal 5-HT receptor antagonists (methysergide) – both 5-HT and NE receptor antagonists were required.

Both PAG and NRM stimulation release NE in spinal cord.

Shown that pathway from PAG to spinal cord involved both medial and adjacent lateral parts of rostral ventromedial medulla.

Stimulation in A6 (locus coeruleus and sub-coeruleus) and A7 (parabrachial/KF) produced NE-mediated inhibition of spinal nociceptive transmission and facilitation of spinal nociceptive transmission is revealed.

Sandkühler & Gebhart 1983

why tail flick? – a spinal nociceptive reflex under tonic inhibitory control.

Ren et al. 1988

Brainstem Organization of Modulatory Currents - current

1. PAG stimulation-produced analgesia
2. No direct PAG to spinal cord projection
3. Descending effects are not only inhibitory.
RVM Modulation of Spinal Transmission

- RVM electrical stimulation
- RVM chemical stimulation:
  - glutamate
  - baclofen
  - neurotensin
  - cholecystokinin
  - opioids

Non-selective and selective chemical stimulation reproduces the effects of electrical stimulation.

Chemical Modulation of Noxious Heat

- RVM chemical stimulation:
  - glutamate
  - baclofen
  - neurotensin
  - cholecystokinin

* all can facilitate spinal transmission

RVM Chemical Modulation of Visceral Nociception

% control

visceromotor response

visceromotor response

time (min)

- 0.03 pmol NT
- 30 pmol
- 300 pmol
- 3000 pmol

Urban and Gebhart, 1997
RVM Modulation of Non-Noxious Brush

Modulation Summary

- RVM is a relay in the pathway for descending influences on spinal nociceptive transmission
- Both inhibitory and facilitatory influences can be activated from the brainstem
- Inhibitory and facilitatory influences are not limited to noxious cutaneous inputs, but apply to non-noxious cutaneous and visceral inputs
- Descending pathways for inhibition are largely contained in the dorsolateral funiculus, those for facilitation in the ventral spinal cord
- Which cells in RVM drive inhibition/facilitation?

The ON- and Off-cell Model (Fields et al., 1983)

- Off cells have a periodic pattern of spontaneous activity. They pause or turn off in advance of withdrawal from a noxious thermal stimulus applied to the tail or hindpaw. Interpreted to represent the RVM inhibitory output cell.
- On cells accelerate firing in advance of withdrawal from a noxious thermal stimulus applied to the tail or hindpaw. Interpreted subsequently to represent facilitatory RVM output, a concept still undergoing discussion.
So, what do ON- and Off-cells do?

• early thinking was that they represented inhibitory and facilitatory outputs from RVM that modulated noxious spinal transmission and that 5-HT was the spinal mediator of inhibition
• current thinking is that ON and OFF cells are not selective modulators of noxious spinal events:
  – only ~ 35% of ON and OFF cells project to the cord
  – the discharge of ON and OFF cells changes in the way described only for noxious thermal stimulation of the skin and not also for noxious mechanical or visceral stimulation
  – the RVM is a major source of descending spinal modulation, affecting neurons of all types to effect sensory, autonomic, and motor adjustments needed to ensure homeostasis (Mason, 2005)

Descending Modulation of Pain – my view

✓ normally, descending modulation is a balance of inhibition and facilitation (*inhibition predominates*)
✓ peripheral tissue insult increases spinal and brainstem neuron excitability (*central sensitization*)
✓ after tissue insult, descending facilitatory influences can gain currency, and in some circumstances ….  
✓ maintain central sensitization

Hypothesis/question: can chronic ‘functional’ disorders be maintained by central mechanisms in the absence of persistent tissue insult?
An Integrated View of Pain Modulation

Disease States:
- Hypertension
- Myocardial Ischemia

Stress
- Pain
- Exercise
- Fear

CNS - Determined States & Behaviors

Physiological Responses
- Arterial Blood Pressure
- Chemoreceptors?

Blood Distribution
- Opioids
- Pulmonary Congestion
- Humoral?
- Kinins?

Somato-visceral stimuli
- Heart & Lungs

Gebhart & Randich 1990

nociceptive/other reflexes