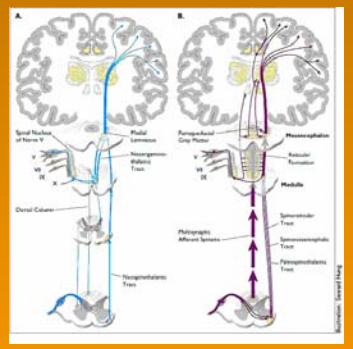
CHEMICAL RELEASES IN ACUPUNCTURE



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Criteria for scientific acceptance

- PHYSIOLOGICAL EFFECT
- ASSESSMENT OF RISK OR TOXICITY
- PILOT STUDIES TO ASSESS POTENTIAL BENEFITS
- LARGE RANDOMIZED CLINICAL TRIALS TO ASSESS EFFICACY
- OUTCOME STUDIES

Physiological Evidence

- ENDOGENOUS OPIOIDS
- ANIMAL MODELS
- MIDBRAIN MONOAMINE EFFECT
- PITUITARY AXIS
- DOPAMINERGIC SYSTEM

Naloxone blocks AA

- PRE-INJECTION WITH NALOXONE BLOCKS EA EFFECT IN MICE
  - Pomeranz, et al, 1976 ***Life Science*** **19**:1757-1762
- PRE-INJECTION WITH NALOXONE BLOCKS AA EFFECT ON DENTAL PAIN IN HUMANS
  - Mayer, et al, 1977, *Brain Research* **121**:368-372

Opioid Receptors and Ligands

Opioid Receptors	Endogenous Agonist	Antagonist
μ (mu)	β-Endorphin	Naloxone
δ (delta)	Met-enkephalin Leu-enkephalin	Naloxone
κ (kappa)	Dynorphin	Naloxone

Confirmation Opioid Hypothesis

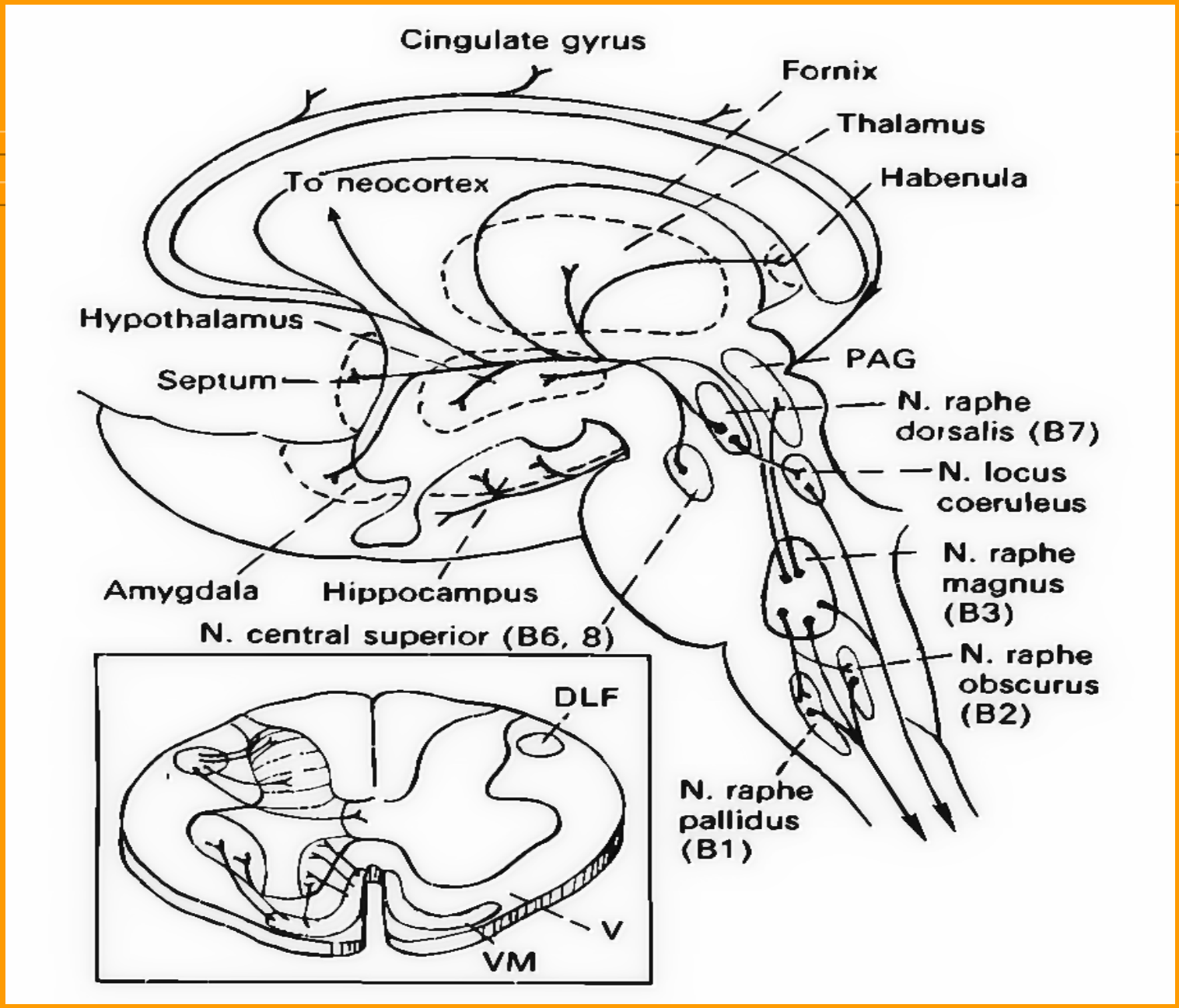
- Naloxone has stereospecific effect
- AA enhanced with use of peptidase inhibitors
- CSF and plasma elevation of β-endorphin
- Differential elevation of opioids in spinal cord
  - Met-enkephalin (low freq EA)
  - Dynorphin (high freq EA)

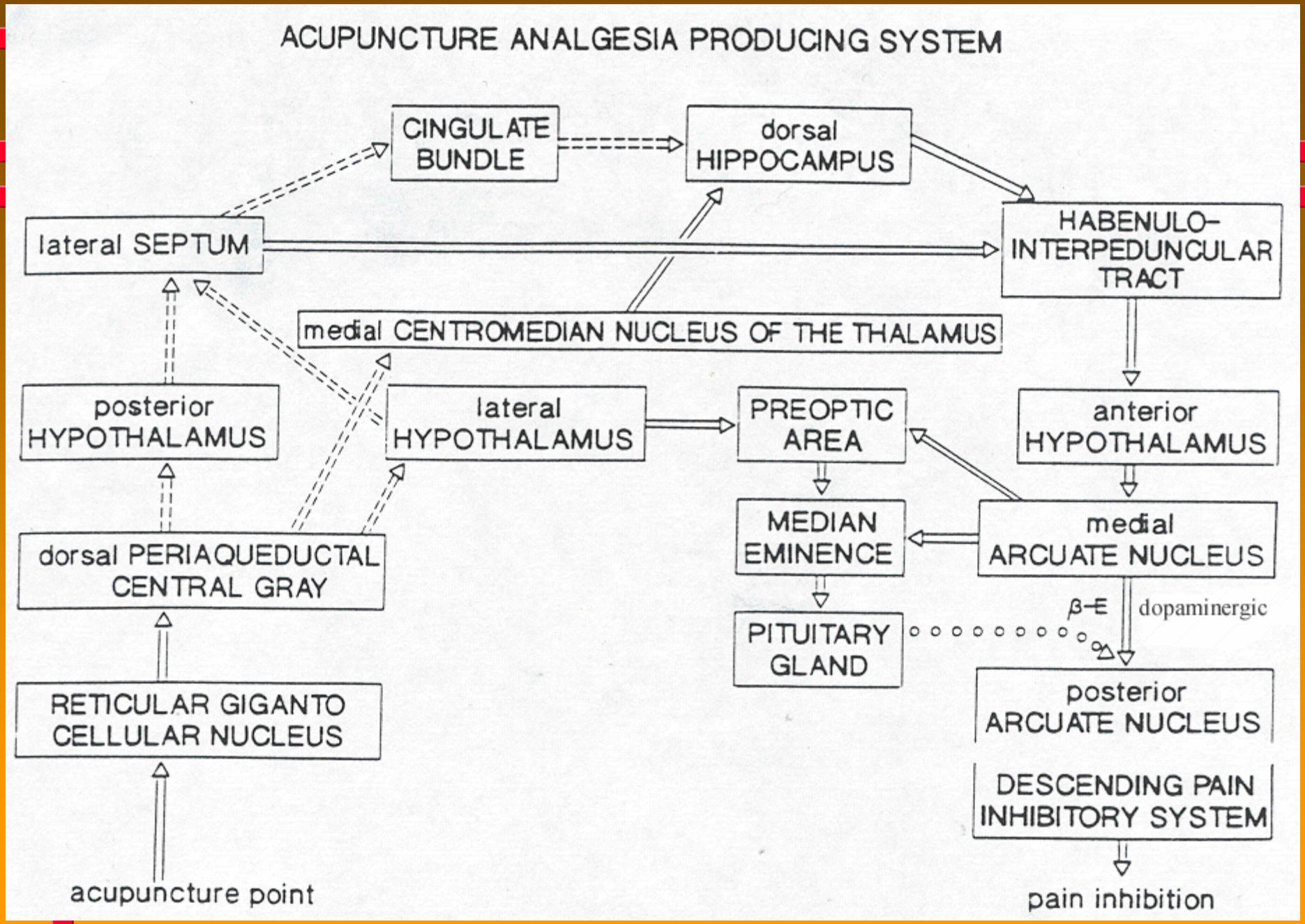
Segmental and Ascending Effect

- AA leads to excitation of ascending pathway via STT
- With Lesion of STT Segmental Inhibitory effect of AA remains
- Both effects linked to release of endogenous opioid peptides

Brain Territories

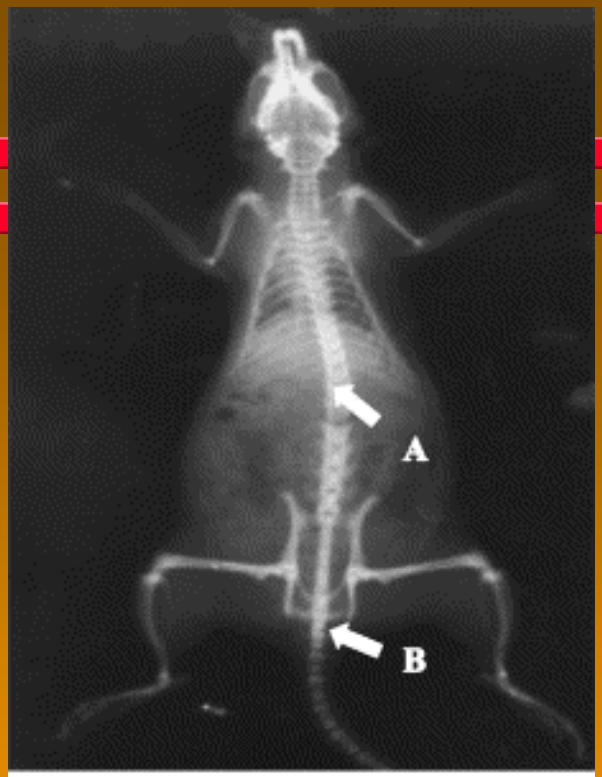
- AA correlates in animal models with rise in opioid peptides in CNS
  - Periaqueductal gray
  - Nucleus Accumbens
  - Amygdala
  - Nucleus caudatus
- Naloxone applied in above regions also inhibited AA

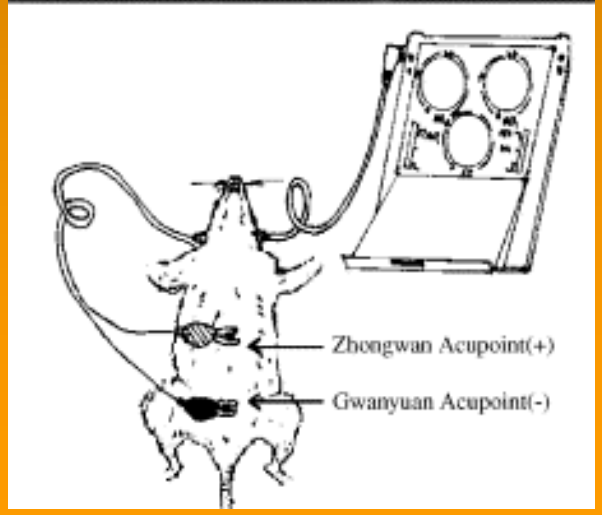

Cingulate gyrus
Fornix
Thalamus
Habenula
To neocortex
Hypothalamus
Septum
PAG
N. raphe dorsalis (B7)
N. locus coeruleus
N. raphe magnus (B3)
N. raphe obscurus (B2)
N. raphe pallidus (B1)
Amygdala
Hippocampus
N. central superior (B6, 8)
DLF
V
VM


ACUPUNCTURE ANALGESIA PRODUCING SYSTEM
CINGULATE BUNDLE
dorsal HIPPOCAMPUS
lateral SEPTUM
HABENULO-INTERPEDUNCULAR TRACT
medial CENTROMEDIAN NUCLEUS OF THE THALAMUS
posterior HYPOTHALAMUS
lateral HYPOTHALAMUS
PREOPTIC AREA
anterior HYPOTHALAMUS
MEDIAN EMINENCE
medial ARCUATE NUCLEUS
dorsal PERIAQUEDUCTAL CENTRAL GRAY
β-E
dopaminergic
PITUITARY GLAND
RETICULAR GIGANTO CELLULAR NUCLEUS
posterior ARCUATE NUCLEUS
DESCENDING PAIN INHIBITORY SYSTEM
acupuncture point
pain inhibition

Further data: Animal models

- Mice deficient in opiate receptors lack AA response
- EA inhibits withdrawal syndrome in mice
- Rats deficient in endorphins lack AA response
- AA effect transfer with cross-circulation of CSF
- Microinjection of endorphin antibodies blocks AA


A
B


Zhongwan Acupoint(+)
Gwanyuan Acupoint(-)

Electrophysiological Studies

- EA in animal models found to activate some PAG neurons and inhibits others
- Only inhibition is Naloxone reversible
- Suggests EA inhibits “inhibitory interneurons” in PAG that are mediated through opioid peptidergic system and releases descending pain modulation

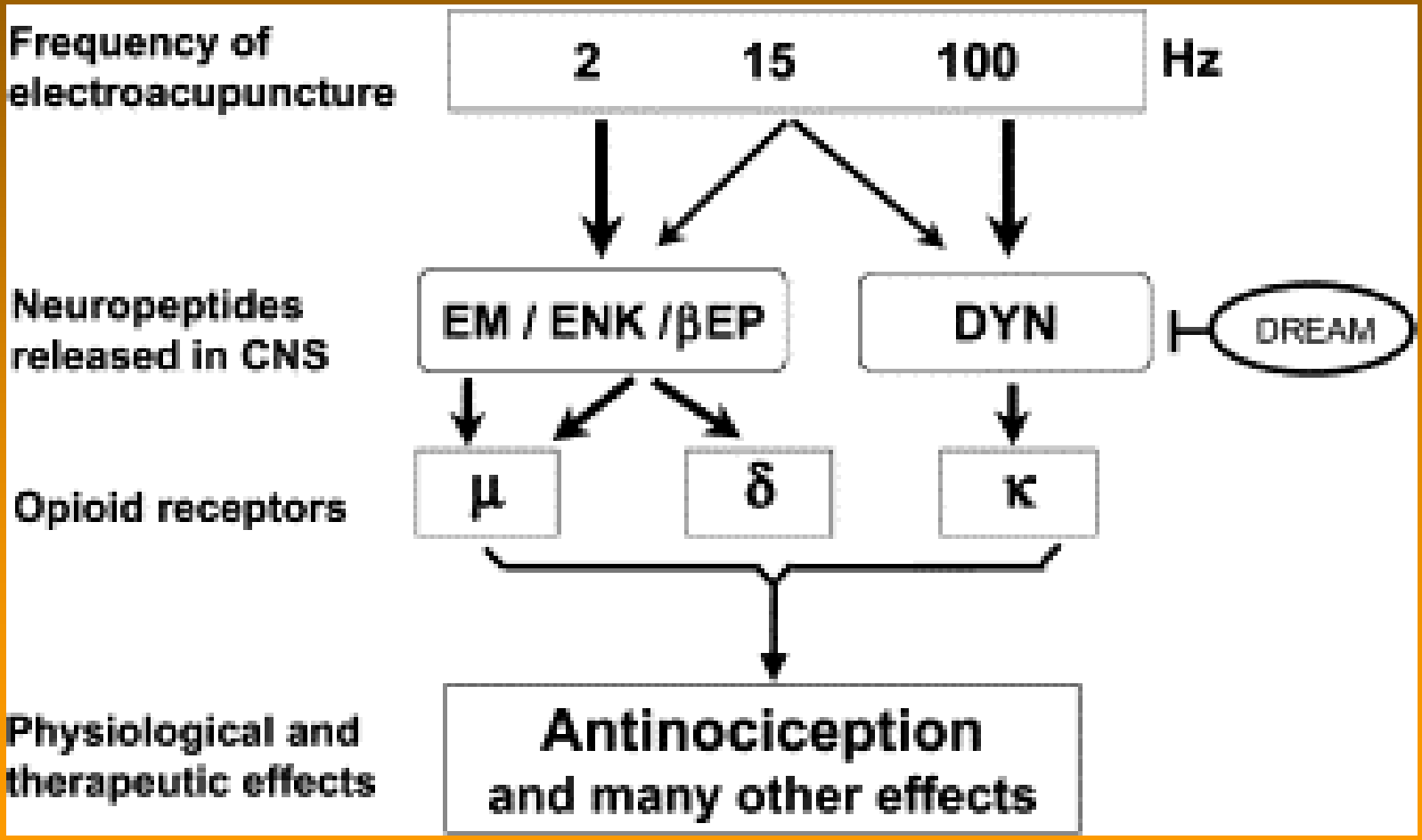
State dependent results

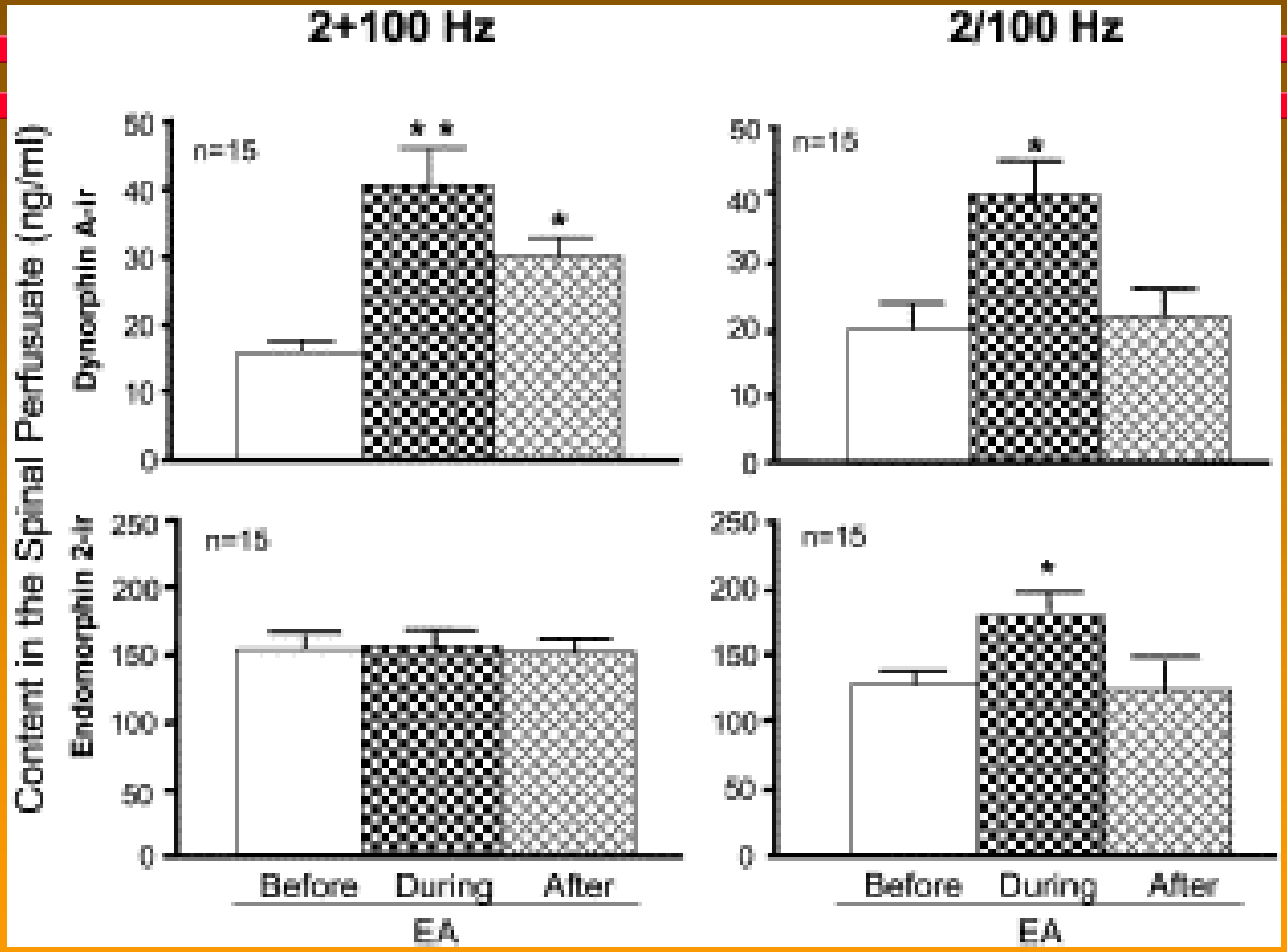
- Efficacy of EA in Chronic Pain Patients with low levels of serum β-endorphin correlated with significant rise in serum levels
- Anovulatory woman showed elevation in serum beta-endorphin with EA
- Normal menstruating woman did not

Sham vs. true AP

- Low frequency EA produces AA, sham EA does not in animal models and human models of acute pain
- Lesioning part of the thalamus (CMN) or posterior Hypothalamus
  - Removes part of analgesic inhibitory system in CNS
  - Sham EA then will produce AA
  - Blocked by antisera to dynorphin but not the enkephalins

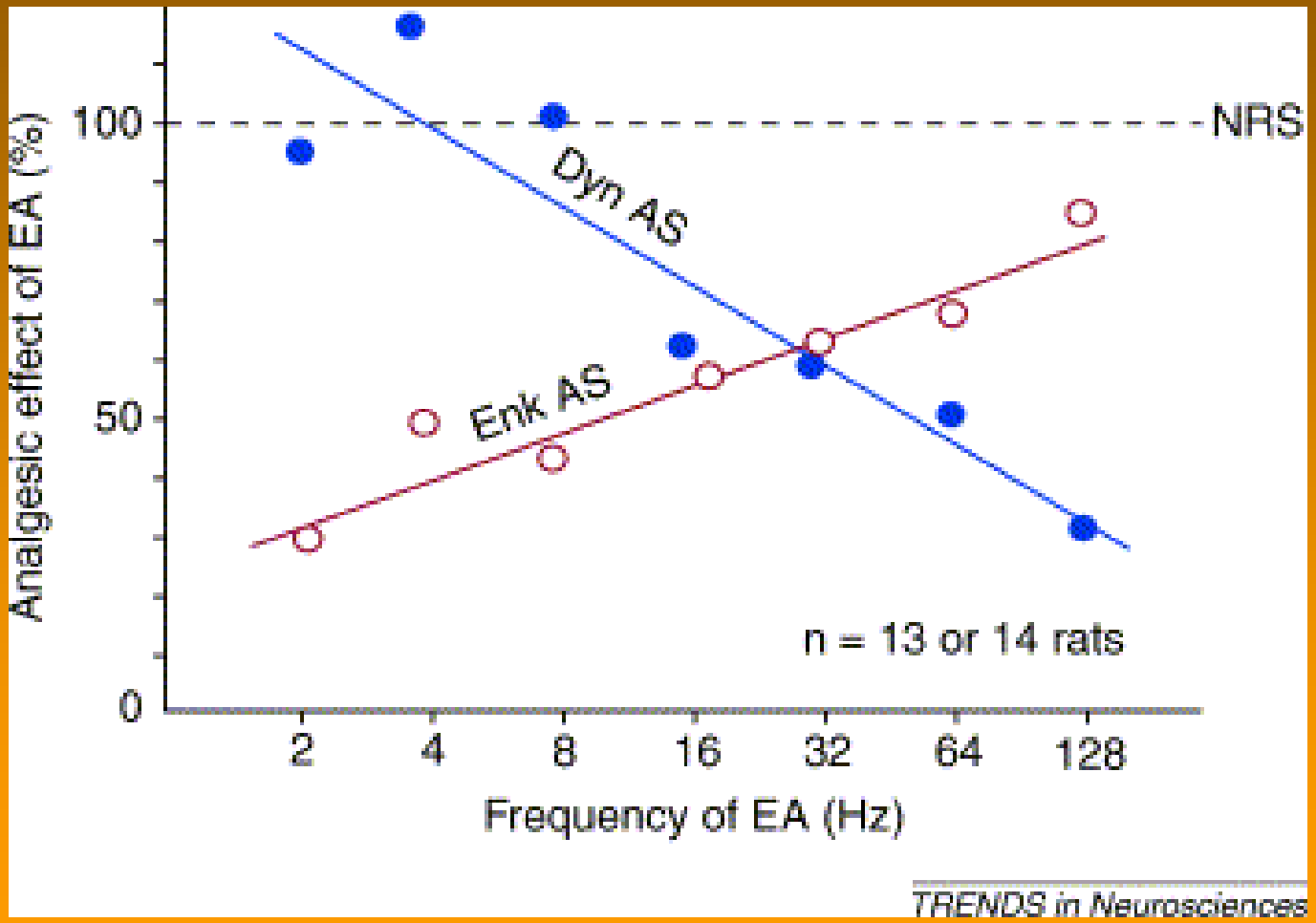
Differential Effect of EA





Han, JS. Neuroscience Letters 2004; 361(1-3):258-261

Anti-sera to endogenous opioids



Han J. Trends Neurosci. 2003 Jan;26(1):17-22.

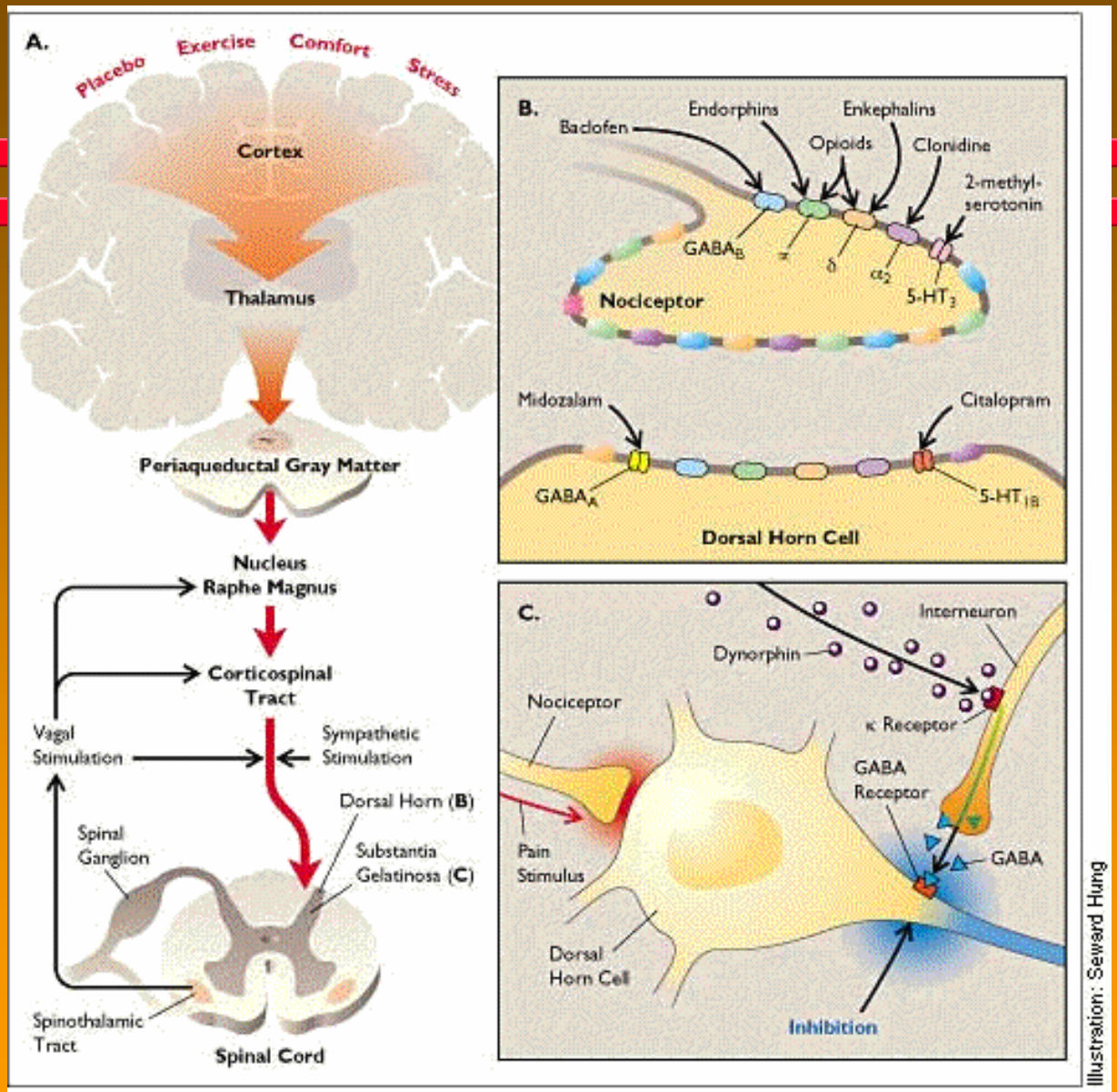
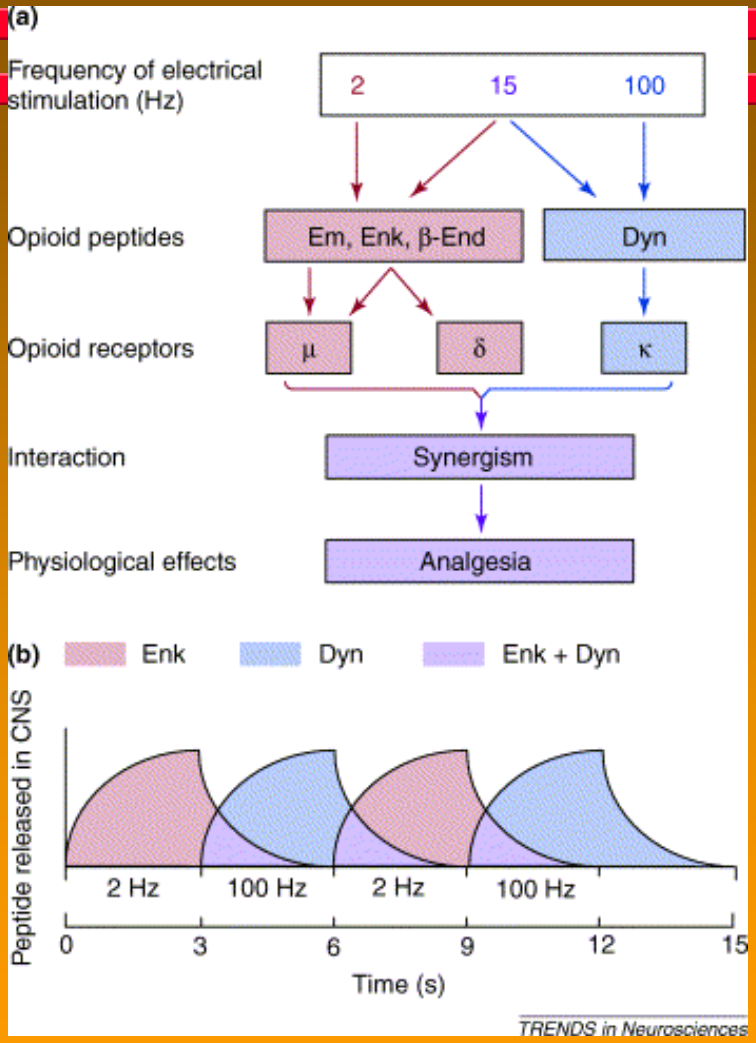
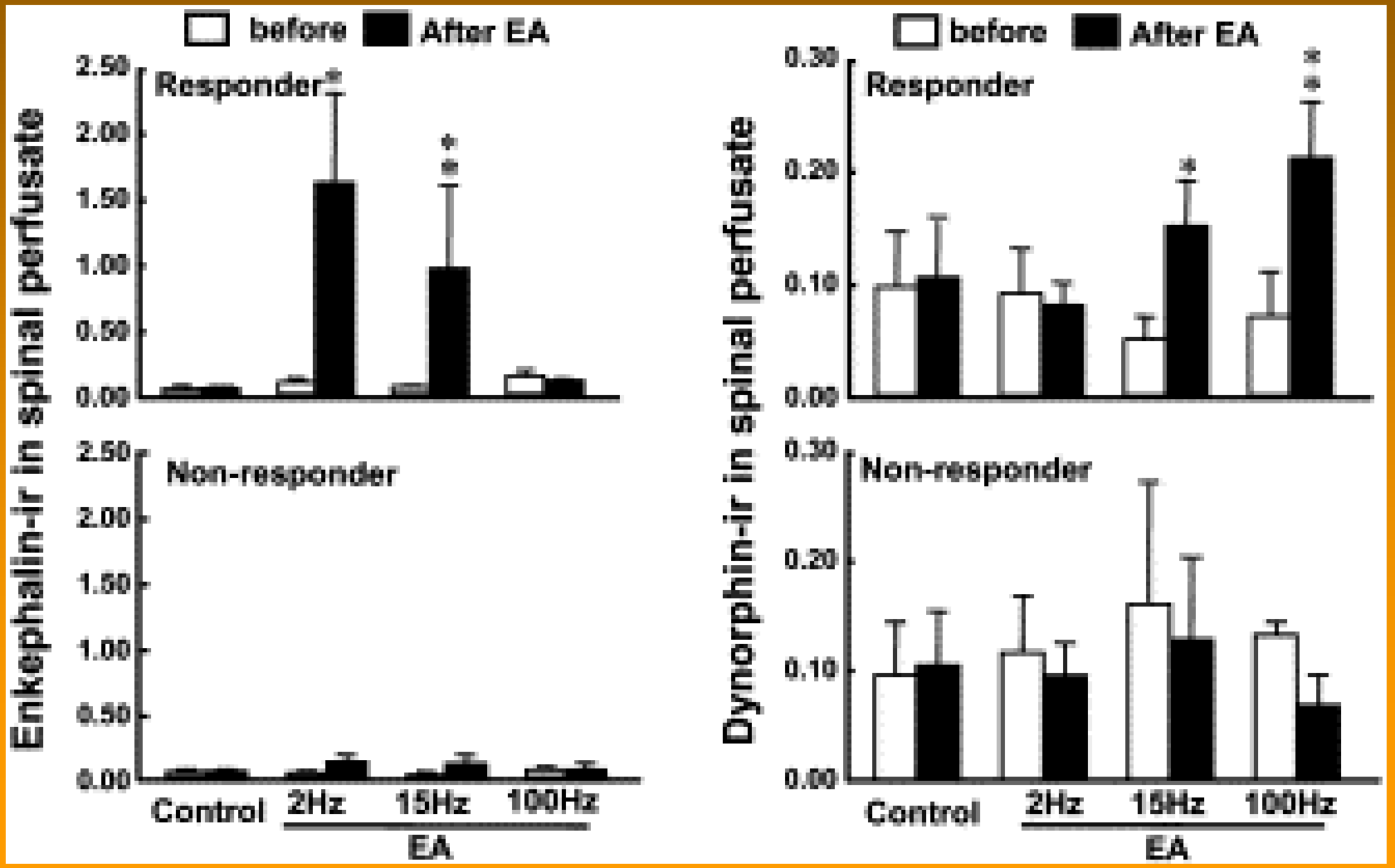


Illustration: Seward Hung



Han J. Trends Neurosci. 2003 Jan;26(1):17-22.

Differences in Rat Response



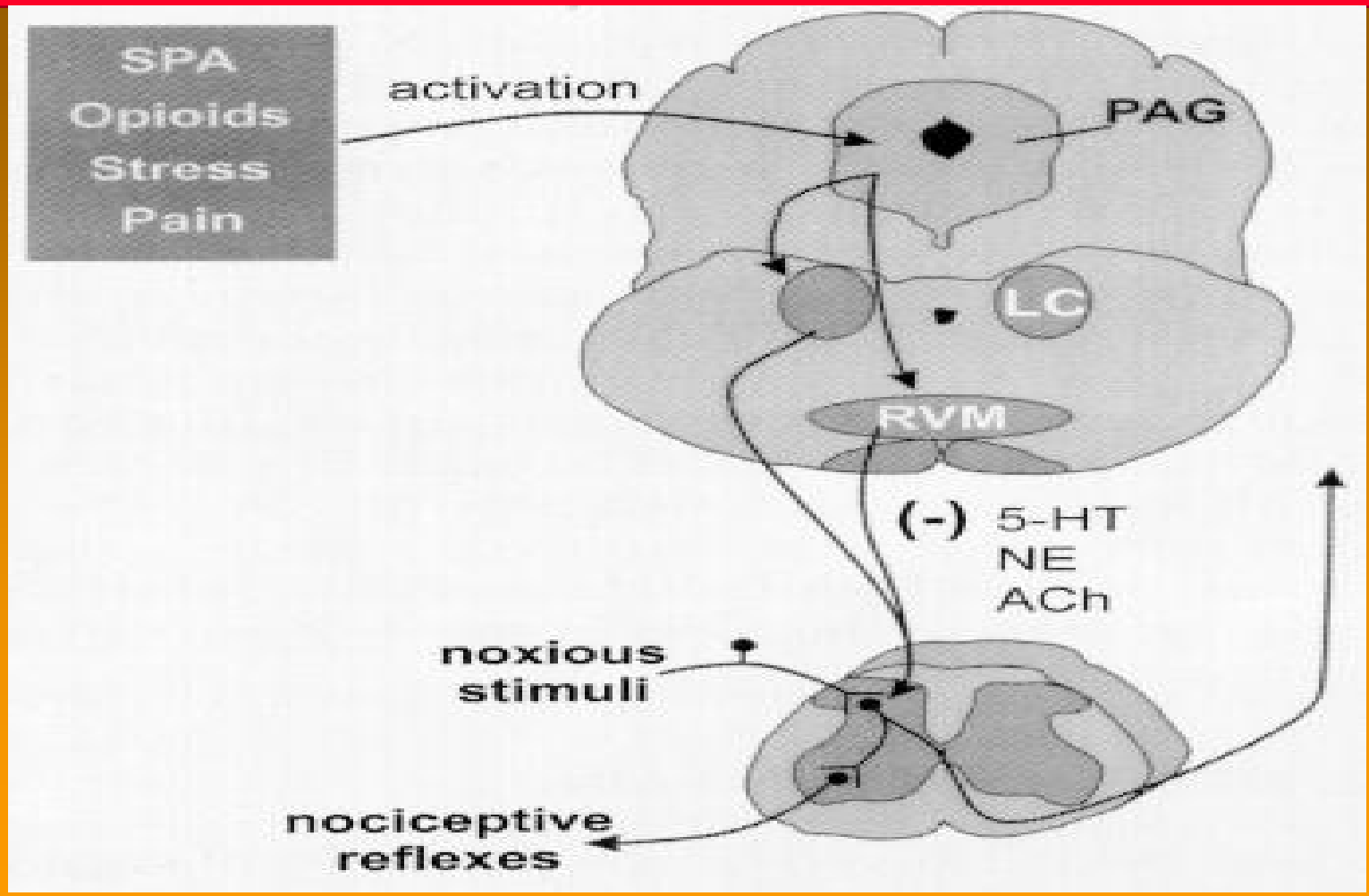
Sites of opioid activity

- β-endorphin effects on arcuate nucleus and PAG, nucleus accumbens, amygdala, nucleus caudatus
  - Sham pts activate lateral PAG
  - True AP activates dorsal PAG
- met-enkephalin and dynorphin sites in the Spinal Cord

Monoamine hypothesis

- Ablation of raphe magnus blocks AA
- Chemical destruction of 5HTP Neurons reduces AA
- Serotonin receptor blockade blocks AA
- Pre-injection with 5HTP enhances AA

Decending inhibition



Enhances serotonin synthesis

- Stimulates hydroxylation, decarboxylation and deamination in metabolism of 5HTP

Catecholamines

- EA reduces NE in the brain of rats and humans due to enhanced metabolism
  - Decreases seen in the Locus Ceruleus, PAG, and Raphe Magnus
- Increases in NE in Spinal Cord
  - Part of descending inhibitory effect

Acetylcholine and dopamine

- Acetylcholine release from Caudate Nucleus is enhanced
  - May inhibit thalamic response to sensory input
- Dopamine antagonizes AA via Caudate nucleus inhibition
- Dopamine may enhance AA via the Arcuate Nucleus

Dopaminergic System

- Dopaminergic System plays a major role in locomotor system
  - Involved with activity-stimulating effects of drugs of abuse
  - Nucleus Accumbens
- Bilateral EA on Heart 7 following 15 days of withdrawal in a Morphine tolerant rat abrogated the dopamine release in Nucleus Accumbens and excess behavioral activity following Morphine challenge
  - Effect not seen with EA on TW 8

Kim MR, et al. Neuroscience Letters 2005;387:17-21.

Pituitary axis

- β-endorphin plasma elevation
- ACTH plasma elevation
- Hypophysectomy abolishes AA

Role of Hypothalmus

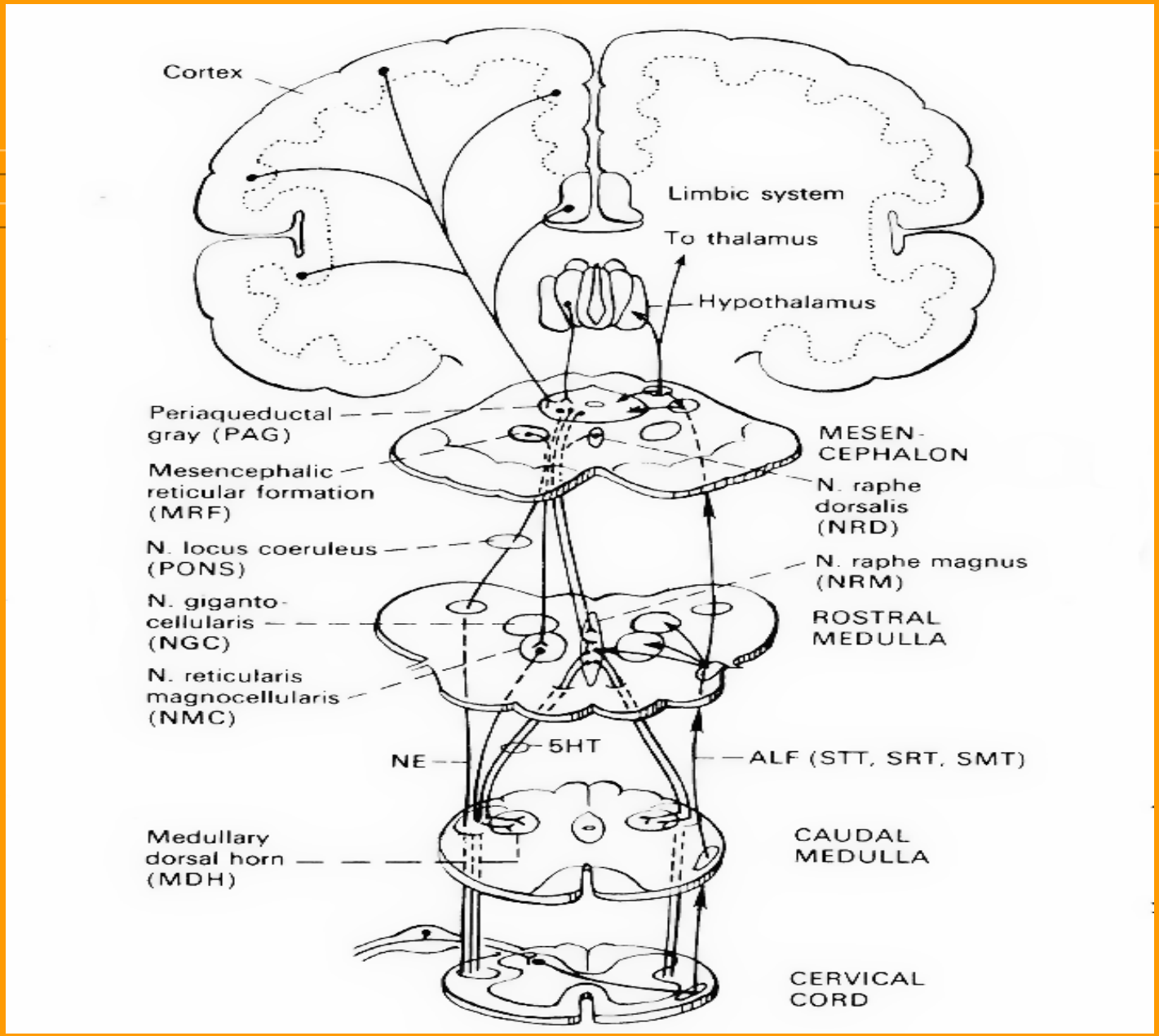
- Likely that median part of Arcuate nucleus is the terminal region in the AA afferent pathway
- Posterior part of Arcuate nucleus is starting region of efferent pathway

Acupuncture vs DNIC

- Differential effect sham vs true AA
  - SHAM EFFECT (DNIC) BLOCKED BY ANTI-SERA DYNORPHIN
  - AA EFFECT BLOCKED BY ANTI-SERA met-ENKEPHALIN
- AA is naloxone reversible in hypothalmus but Sham stimulation is dexamethasone reversible
  - Pain vs Stress response
- AA elicited in anesthetized and decerebrate cats
  - Not just the anticipation of pain relief or experiential effects of touch
- Clinical effects longer lasting than DNIC

Proposed neural mechanism

- PUNCTURE RESPONSE
  - A-delta Nerve Fibers (Skin)
  - Type II and III (and IV?) Nerve Fibers (Muscle)
- CENTRAL PROJECTIONS
  - Segmental Effects at Spinal Cord
  - Midbrain (Raphe Nucleus, PAG)
  - Pituitary-Hypothalamus Adrenal Axis


Cortex
Limbic system
To thalamus
Hypothalamus
Periaqueductal gray (PAG)
MESEN-CEPHALON
Mesencephalic reticular formation (MRF)
N. raphe dorsalis (NRD)
N. locus coeruleus (PONS)
N. raphe magnus (NRM)
N. giganto-cellularis (NGC)
ROSTRAL MEDULLA
N. reticularis magnocellularis (NMC)
NE
5HT
ALF (STT, SRT, SMT)
Medullary dorsal horn (MDH)
CAUDAL MEDULLA
CERVICAL CORD

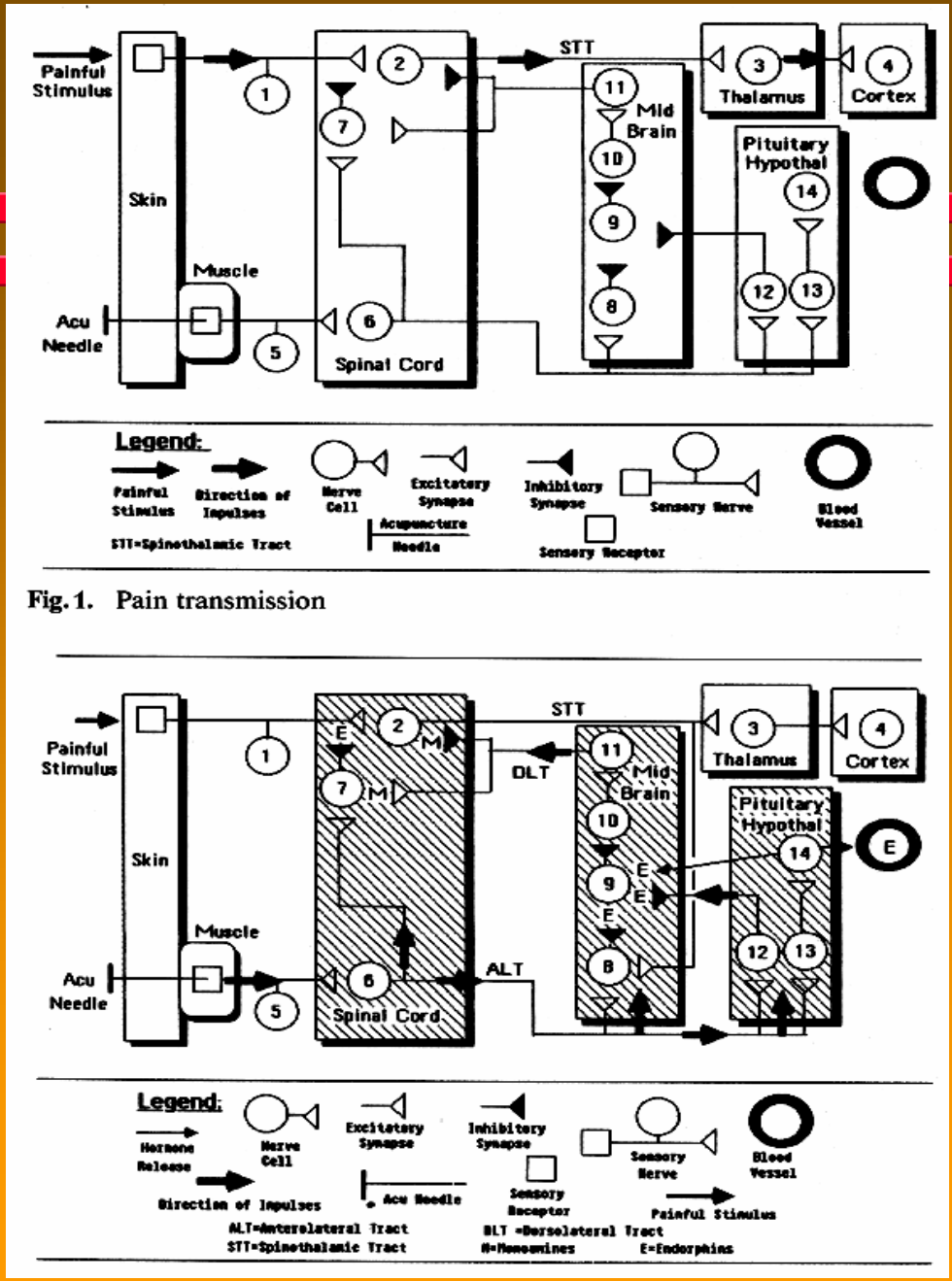
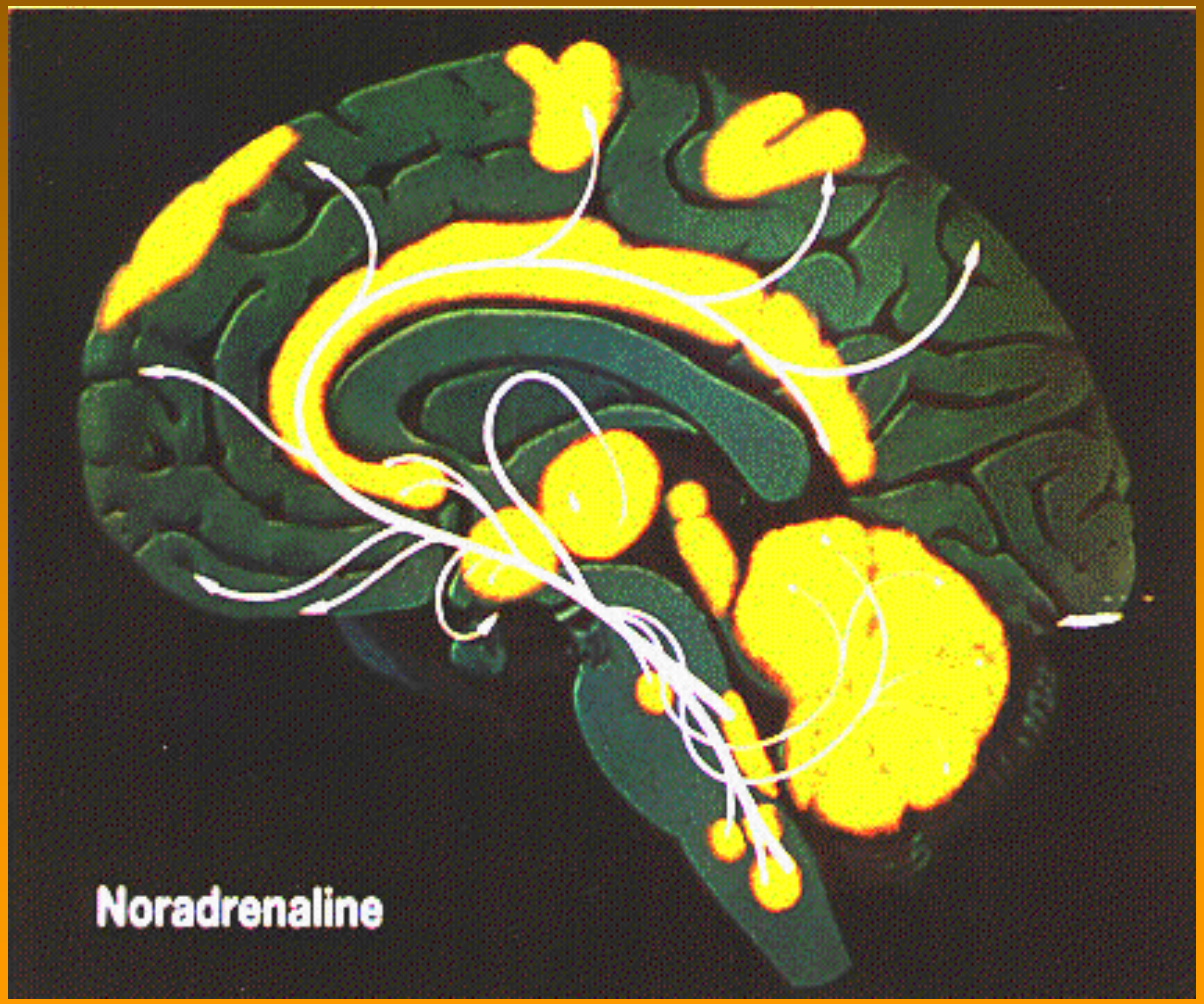


Fig. 1. Pain transmission

Close to Home

John McPherson

With the help of acupuncture, ~~Joe~~ was able to trim 11 strokes off his game.

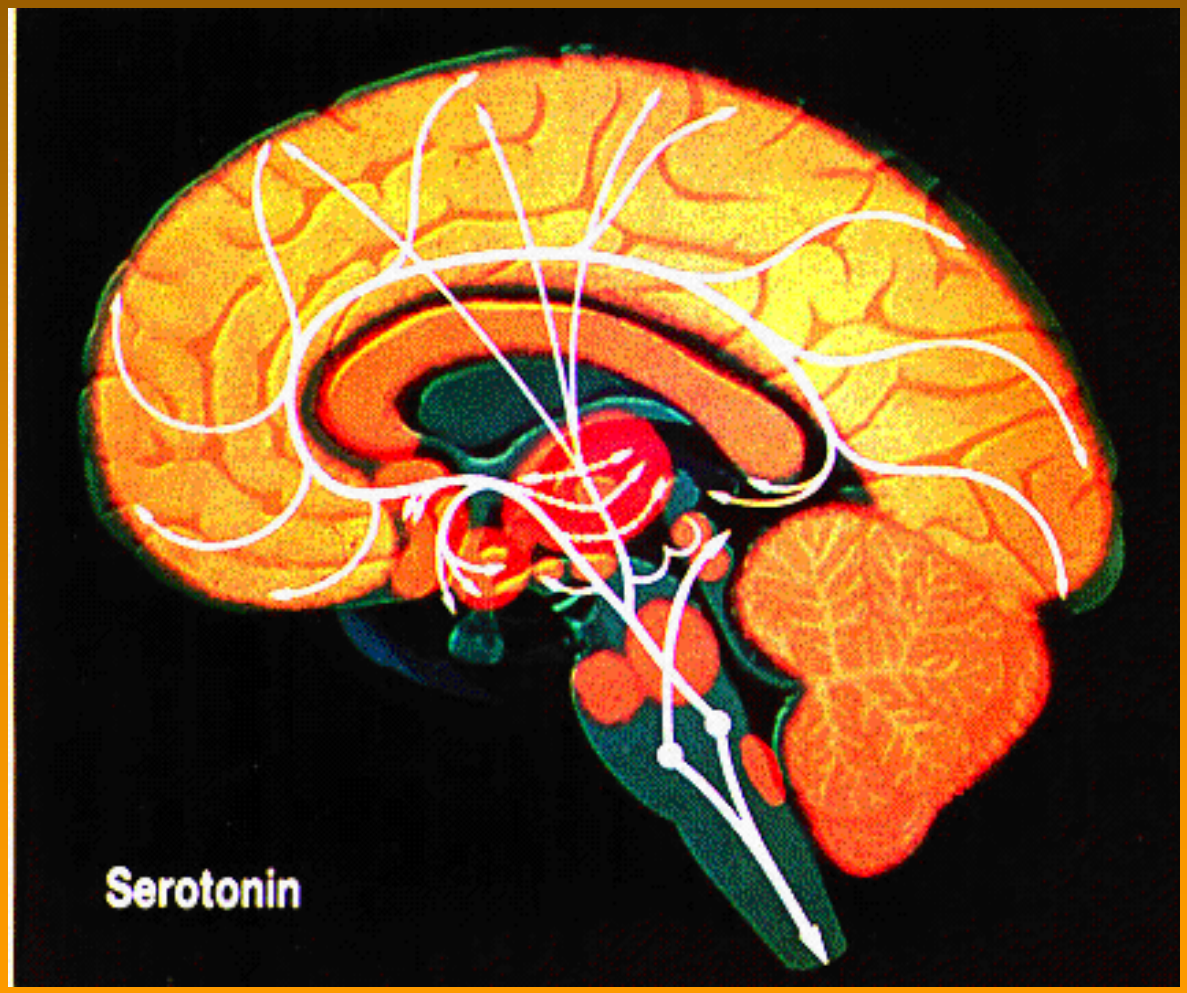

Noradrenaline

Norepinephrine

- Largest site of synthesis is locus ceruleus, in midbrain -- just a few hundred cell, they send axons to almost every other region of the nervous system.
- Another site is lateral tegmental area, with projections which overlap those of the LC but which target the hypothalamus.

NE Functions

- Wide projections of NE system make it ideal for gain-control of other neural systems.
  - NE's modulating action in CNS is primarily inhibitory.
  - In the sympathetic nervous system norepinephrine has an excitatory effect. Released by nerves in internal organs, including the gut, spleen, and heart.
  - Involved in many general functions, like sleep, wakefulness, vigilance, emotion, neuroendocrine function, temperature regulation.
  - Catecholamine theory of depression (antidepressants work on NE -- MAOI's, tri-cyclics, reserpine, etc)

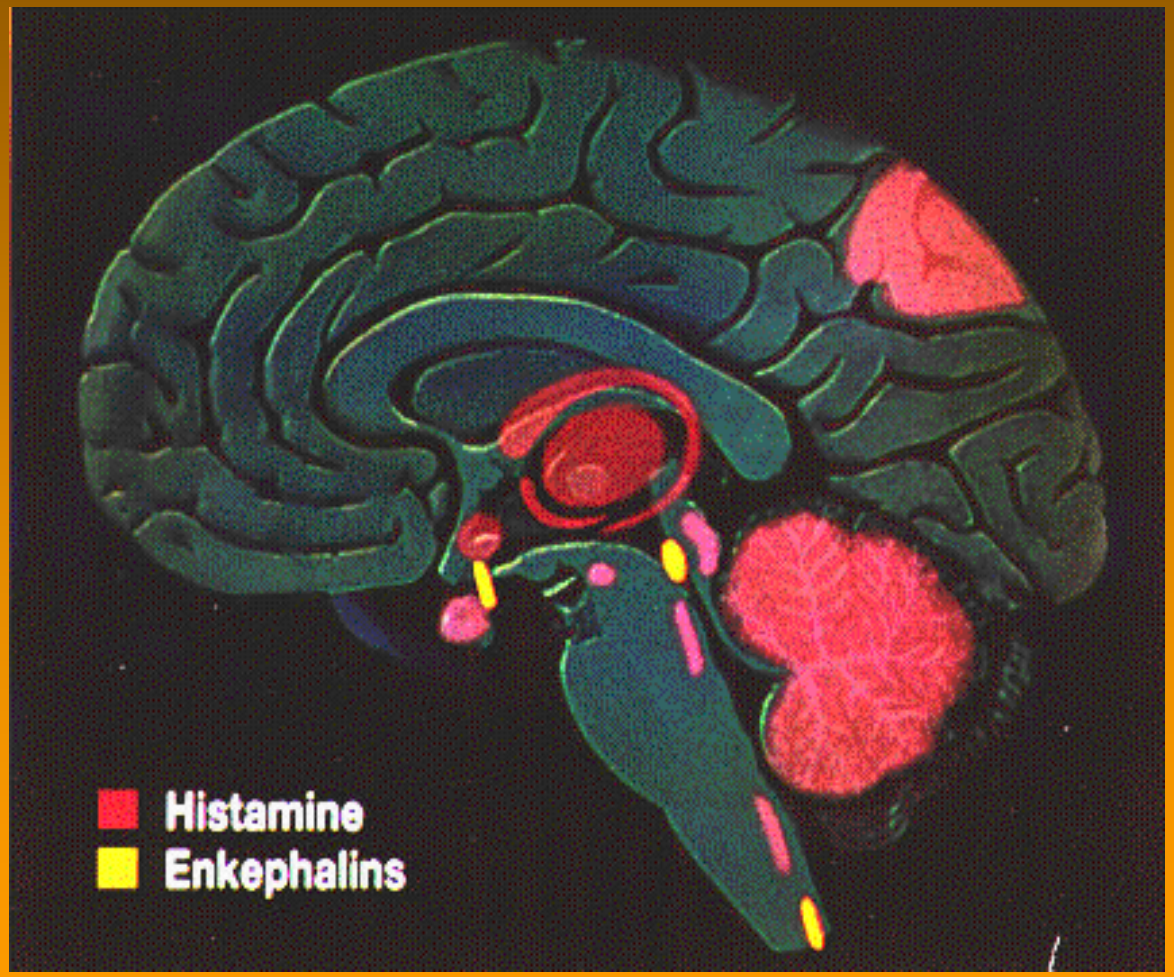

Serotonin

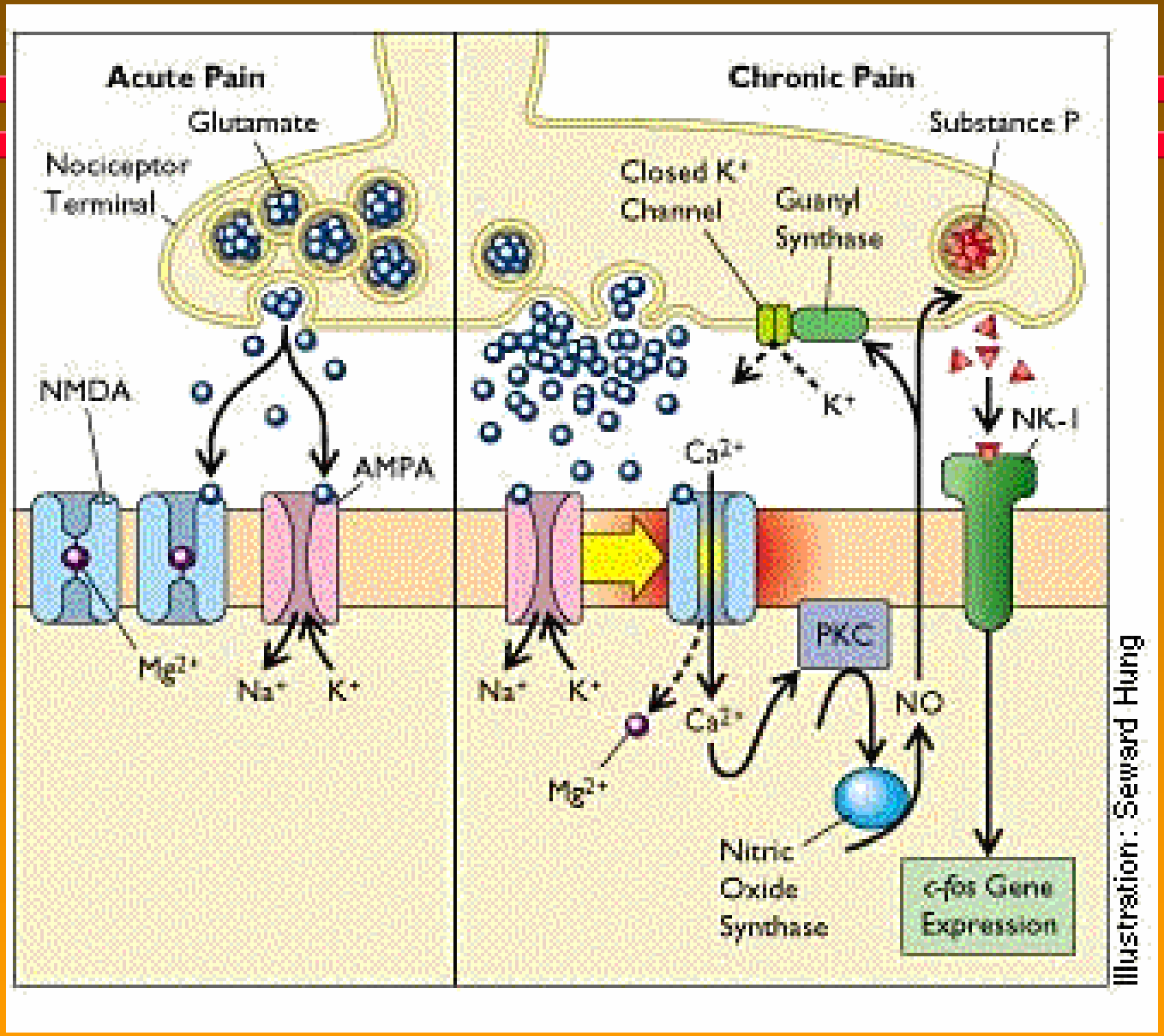
Serotonin

- Synthesized mostly in midbrain, at raphe and in medulla, but has wide projection, much like NE. Highest concentration in pineal.

5HT Functions

- Mostly inhibitory effects on the post-synaptic membrane.
  - Like NE, has widespread influence over sleep (suppresses REM sleep) arousal, sensory perception, including pain, emotion (particularly mood) and higher cognitive functions.
  - LSD is antagonist, on 5HT-2 receptors (one theory of LSD is that it acts at Serotonin receptors to produce dreaming during wakefulness). Suicide victims have low serotonin levels
  - Serotonin undergoes daily variations in level: like melatonin, high in day, low at night.


Histamine
Enkephalins


Acute Pain
Glutamate
Nociceptor Terminal
NMDA
AMPA
Mg^{2+}
Na^+
K^+
Chronic Pain
Substance P
Closed K^+ Channel
Guanyl Synthase
K^+
NK-1
Ca^{2+}
PKC
Na^+
K^+
Ca^{2+}
NO
Mg^{2+}
Nitric Oxide Synthase
c-fos Gene Expression
Illustration: Seward Hung

Conclusions

- Chemical Releases with Acupuncture Analgesia just an epiphenomenon
  - Reflects that physiological changes are occuring but does not help us understand how acupuncture is actually modifying disease and causing long lasting effects.
- Methodology does not allow us to understand the effect of acupuncture on gene regulation
  - Fails to comprehend the more modern understandings about the neuroplastic changes that take place in the nervous system in persistent pain states or disease states and how acupuncture may be able to modify those states by reversing these neuroplastic changes.