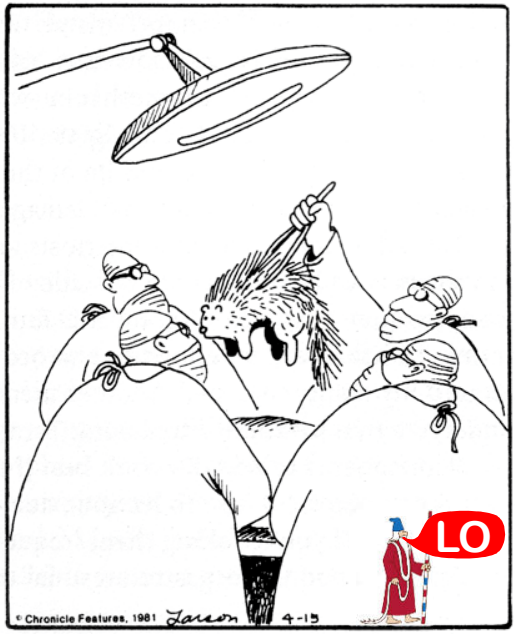
Pain



"Well, I guess that explains the abdominal pains."

"Pain is a component of virtually all clinical strategies, and management of pain is a primary clinical imperative. Opioids are a mainstay of pain treatment."

Goodman & Gilman, 12th edition

Opioid ~~Analgesics~~

Addiction

Opioid ~~Analgesics~~ Addiction

The Dividend, 1916

F.D.A. Likely To Add Reins On Painkillers

By SABRINA TAVERNISE

Trying to stem the scourge of prescription drug abuse, an advisory panel of experts to the Food and Drug Administration voted on Friday to toughen the restrictions on painkillers like Vicodin that contain hydrocodone, the most widely prescribed drugs in the country.

The recommendation, which the drug agency is likely to fol-

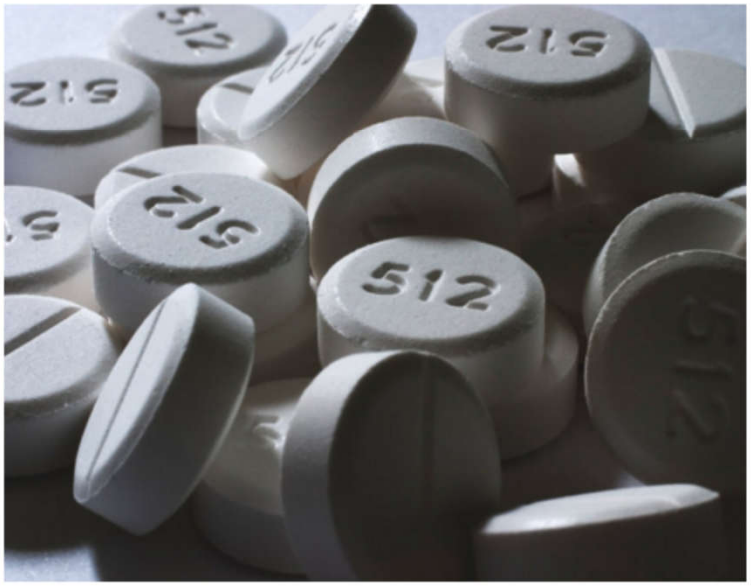
January 26, 2013 • New York Times

Opioid ~~Analgesics~~ Addiction

HEALTH

C.D.C. Painkiller Guidelines Aim to Reduce Addiction Risk

By SABRINA TAVERNISE MARCH 15, 2016



WASHINGTON — In an effort to curb what many consider the worst public health drug crisis in decades, the federal government on Tuesday published the first national standards for prescription painkillers, recommending that doctors try pain relievers like ibuprofen before prescribing the highly addictive pills, and that they give most patients only a few days' supply.

New York Times, March 2016

Opioid ~~Analgesics~~ Addiction

Young Victims of the Opioid Epidemic

By THE EDITORIAL BOARD JAN. 16, 2017

Lilli Carré

New York Times, January 2017

Opioid ~~Analgesics~~ Addiction

Young Victims of the Opioid Epidemic

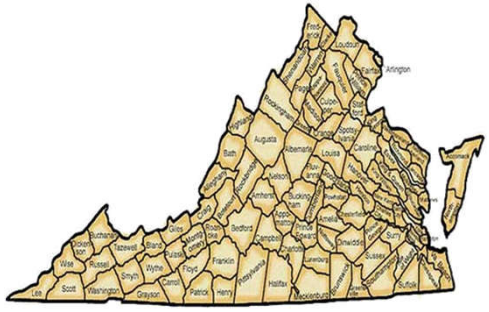
By THE EDITORIAL BOARD JAN. 16, 2017

‘I couldn’t manage the pain’

‘This compound is very sneaky’

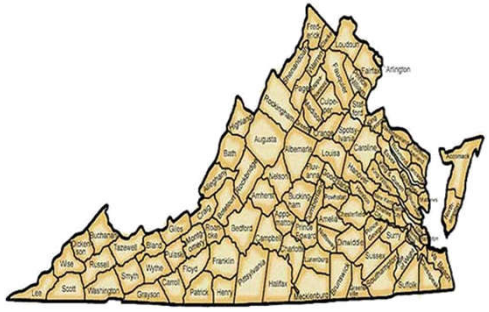
‘I believed the doctors would know better’

New York Times, January 2017



Opioid ~~Analgesics~~
Addiction

In 2014, for the first time in Virginia, more people died from opioid overdoses than fatal car accidents.



Opioid ~~Analgesics~~
Addiction

three Virginians die from drug overdose and more than two dozen are being seen in emergency departments every day due to drug overdose.

Opioid ~~Analgesics~~
Addiction

Young Victims of the Opioid Epidemic

By THE EDITORIAL BOARD JAN. 16, 2017

‘We need them’

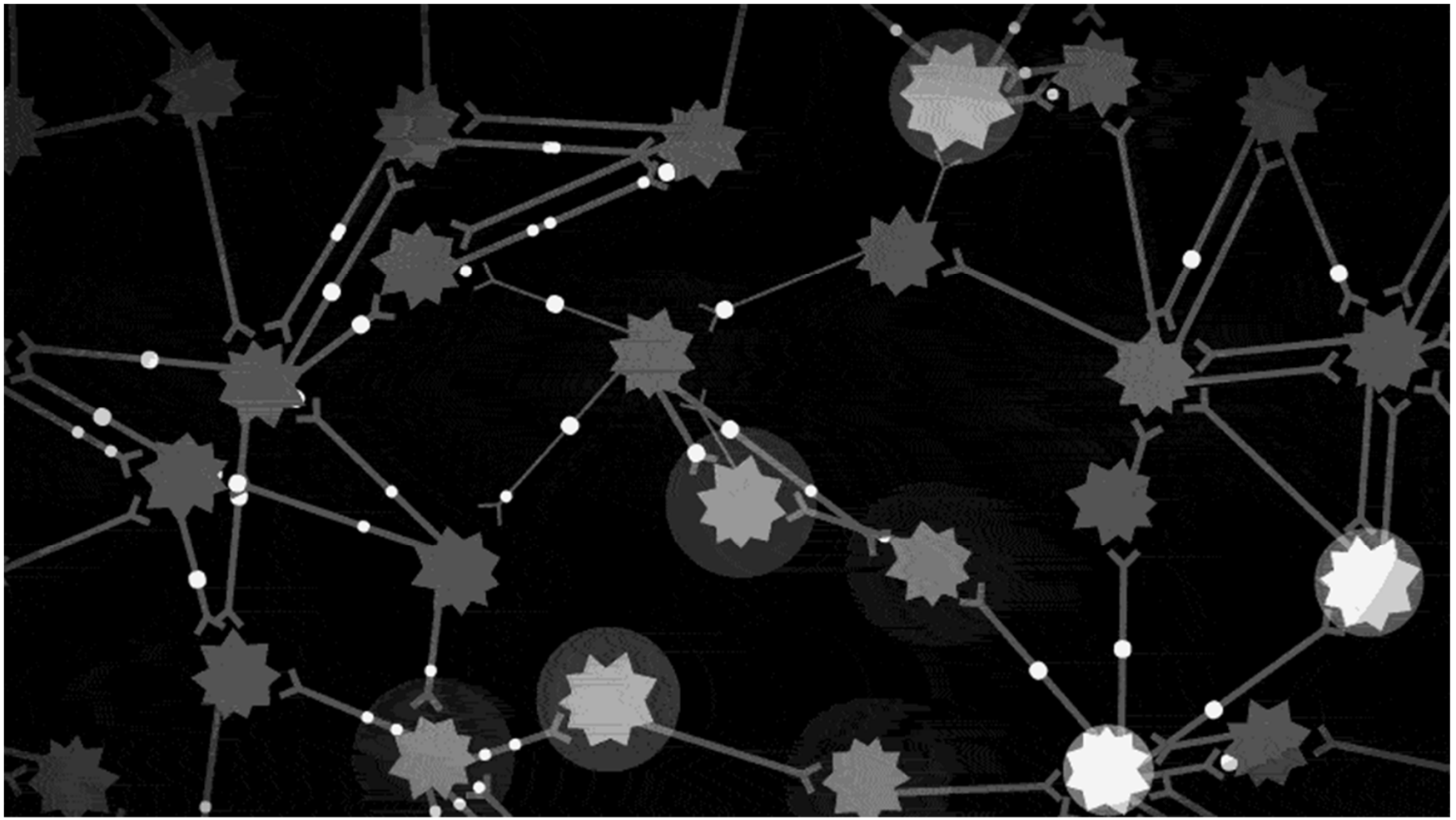
The reporting is one-sided and leaves out how all of these new laws affect chronic-pain patients. We do not abuse these drugs. We need them to function in daily life. Politicians should not make health care decisions. — ***Christiane Warren***, *Kearny, N.J.*

New York Times, January 2017

Opioid ~~Analgesics~~

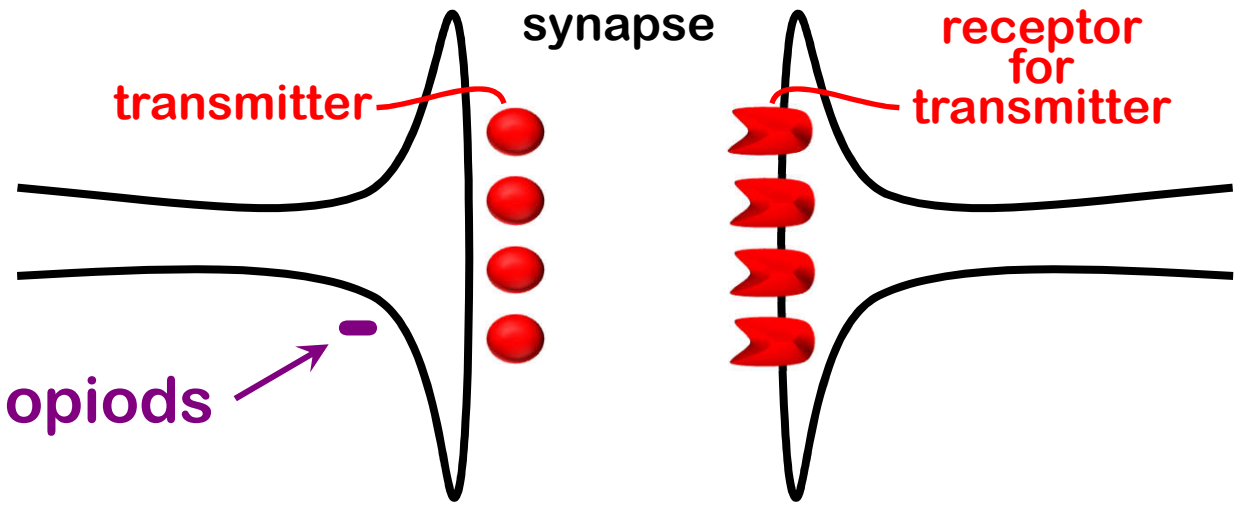
Addiction

Neurons & Activity

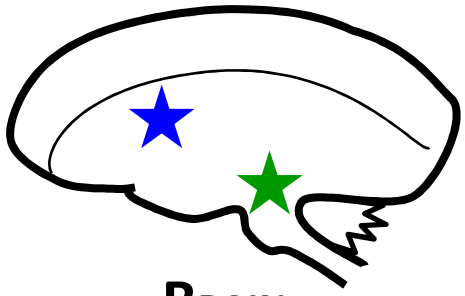


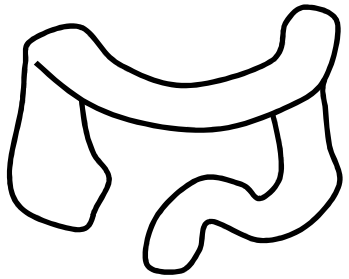
Neurons & Activity

A. Neuronal Communication



B. Plug into Your Favorite Body Part





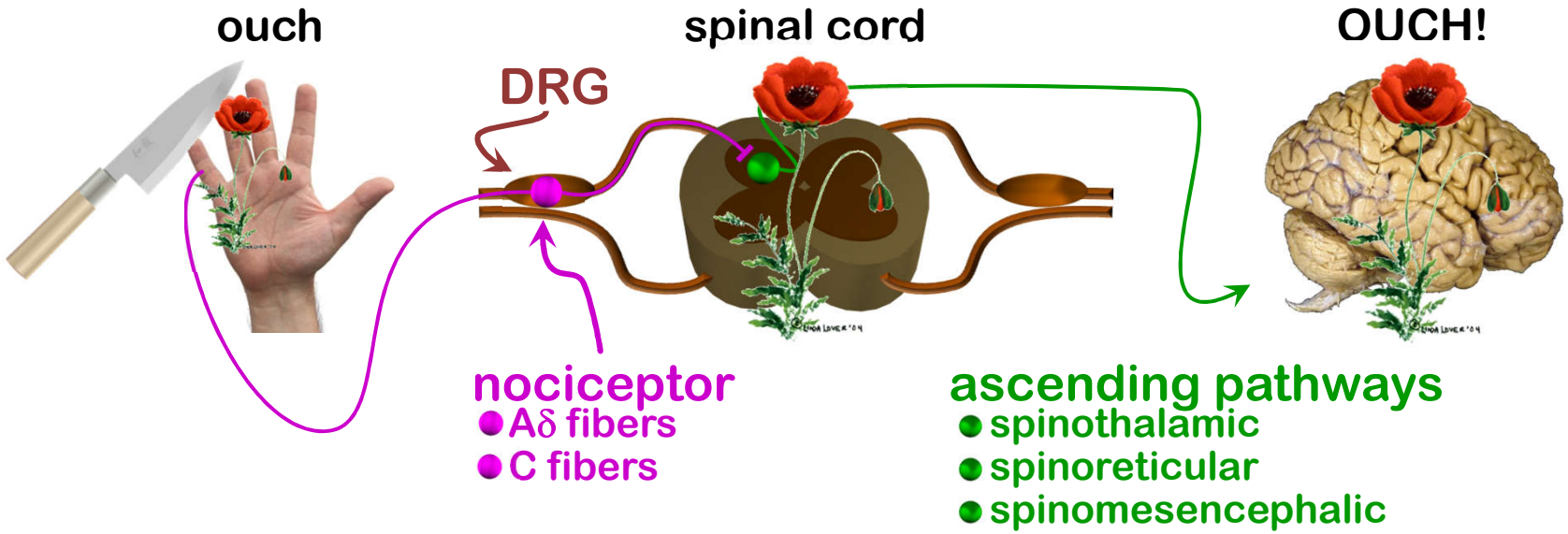
"Opioid" Analgesics

Papaver somniferum

- "opiate": compounds structurally related to products found in opium.
  - natural plant alkaloids
  - semi-synthetic derivatives
  - endogenous peptides (e.g. endorphins)
- "opioid": any substance, regardless of structure that has functional/pharmacological properties of an opiate.
- "narcotic": derived from Greek word narkotikos for benumbing or stupor. Word now associated with opiates and often used in legal contexts.

Pain

- pain: perception of aversive/unpleasant sensation.
  - nociception: transmission of signals to CNS that provide info about tissue damage.



- pains
  - acute nociception
  - tissue injury
    - factors released in injury site (e.g. prostaglandins, bradykinin,etc) activate Aδ fibers
    - hyperalgesia (mildly warm water on a sunburn)
  - nerve injury
    - may involve low-threshold afferents (i.e. Aβ fibers)

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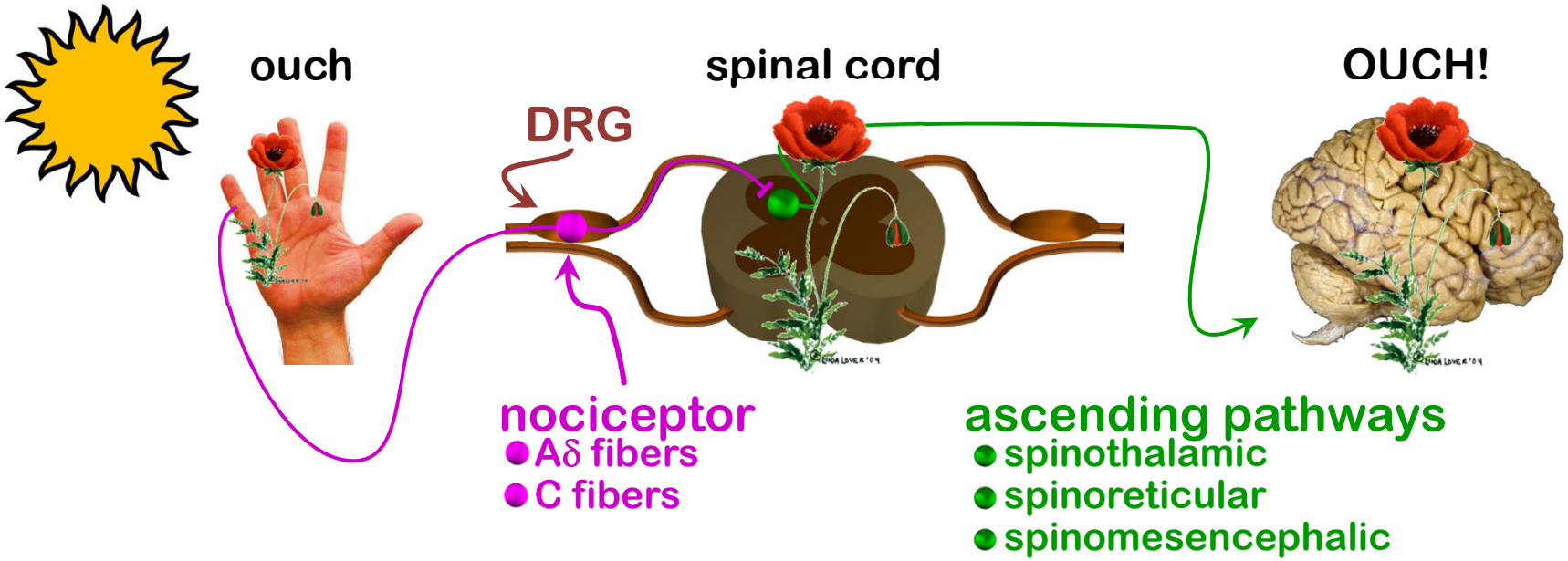

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Opioids & Receptors

Endogenous Opioids

- 3 primary families:
  - endorphins
    - major peptide: β-endorphin
    - precursor: prepro-opiomelanocortin (POMC)
  - enkephalins
    - major peptides: met-enkephalin & leu-enkephalin
    - precursor: proenkephalin
  - dynorphins
    - major peptides: dynorphin A, dynorphin B & neoendorphin
    - precursor: prodynorphin

Receptors

- 3 receptor types (all GPCRs):
  - μ (MOR)
  - δ (DOR)
  - κ (KOR)
- Widely distributed in the CNS
  - Not surprising considering profound effects opioids have on CNS function

Receptor Distribution
Forebrain

Region	Receptors μ: Density of labelled neurons	μ: Grain density per labelled neuron	κ: Density of labelled neurons	κ: Grain density per labelled neuron	δ: Density of labelled neurons	δ: Grain density per labelled neuron
Prefrontal cortex						
Layer I	0	0	0	0	0	0
Layer II	0	0	++	+–++	++–+++	+
Layer III	++	++	+–++	+–++	++–+++	+–++
Layer IV	++	++	0	0	+++	+–++
Layer V	+++	++	+++	++–+++	+–++	+
Layer VI	++	+–+++	+++	++	+	+–++
Occipital cortex, area 17						
Layer I	0	0	0	0	0	0
Layer II	+	+	+	+–++	+++	+
Layer III	+	+	+	+	+++	+
Layer IV	+	+	0	0	+++	+
Layer V	0	0	++–+++	+–++	+–++	+–++
Layer VI	0	0	++	+	+–++	+–++
Hippocampus						
Dentate gyrus	+–++	+	+++	++	+++	++–+++
CA1	+–++	++–+++	+	++	+	+–++
CA2	++	++–+++	+	++	++	++
CA3	++	+++	++	++	+	++
CA4	+++	+–++	+	++	+	+
Striatum						
Accumbens nucleus	+++	++–+++	+++	++	+++†	+++
Putamen anterior part	+++	++–+++	+++	+–++	++†	+++
Putamen posterior part	++	+–++	++	+–++	++†	+++
Caudate nucleus anterior part	+++	++	+++	+–++	++†	+++
Caudate nucleus posterior part	++	+–++	++	+–++	++†	+++
Ventral pallidum	+++	++–+++	++	+	++	+++
Globus pallidus external	++	++–+++	0	0	+–++	++
Globus pallidus internal	+	++	0	0	0	0
Claustrum	+	+	++++	+++–++++	0	0
Basal nucleus of Meynert	+++	++–+++	0	0	0	0

Peckys & Landwehrmeyer, 1999

Receptor Distribution
Midbrain

Region	Receptors μ: Density of labelled neurons	μ: Grain density per labelled neuron	κ: Density of labelled neurons	κ: Grain density per labelled neuron	δ: Density of labelled neurons	δ: Grain density per labelled neuron
Substantia nigra						
Pars compacta	++[†]	+++	+++[‡]	++–+++	0	0
Pars reticulata	+	+–++	+	+	0	0
Central inferior collicular nucleus	++–+++	++–+++	0	0	0	0
Periaqueductal gray	+++	++–+++	++–+++	+++	0	0
Trochlear nerve nucleus	0	0	+	++	0	0
Pontine nuclei	0	0	++++	++	++++	++
Tegmental pedunculopontine nucleus	++–+++	++–+++	0	0	0	0
Locus coeruleus						
Pigmented neurons	0	0	0	0	0	0
Pars alpha	++[§]	+++	+[¶]	+++	0	0
Reticular formation						
Gigantocellular nucleus	0	0	+–++	+–++	0	0
Reticular pontine nuclei	+++	+++	+	+	0	0
Lateral lemniscal nucleus	++	+++–++++	++	++	0	0
Raphe nuclei	++	+++	+++	++–+++	0	0
Parabrachial nucleus	+++	+++	0	0	0	0
Paralemniscal nucleus	++–+++	++–+++	0	0	0	0
Dorsal vagal nerve nucleus	++–+++	++–+++	+–++	++	+	+
Solitary tract nucleus	+++	++–+++	++	+++	+	+
Gracile nucleus	0	0	+	+	+	+
Cuneate nucleus	0	0	0	0	+	++
Spinal tract trigeminal nerve nucleus	++++	+++–++++	++++	+++	+++	++
Ambiguus nucleus	++++	+++	++++	+++	+	+
Retroambiguus nucleus	++	+++	0	0	0	0
Inferior olivary nucleus	+	+–++	0	0	0	0
Medial accessory olivary nucleus	+	+–++	0	0	0	0
Arcuate nucleus	0	0	++++	++–+++	++++	++–+++
Supraspinal nucleus	0	0	++	+++	0	0
Accessory nucleus	++	++–+++	0	0	0	0
Cerebellum						
Granular layer	++++	++	+++	++	0	0
Golgi cells	++–+++	++–+++	++–+++	++–+++	++–+++	+–++

Peckys & Landwehrmeyer, 1999

Receptor Distribution
Spinal Cord

	Receptors					
	μ		κ		δ	
Region	Density of labelled neurons	Grain density per labelled neuron	Density of labelled neurons	Grain density per labelled neuron	Density of labelled neurons	Grain density per labelled neuron
Dorsal horn	+–++	++	+	+–++	0	0
Substantia gelatinosa	++–+++	++	+–++	+–++	0	0
Zona intermedia	+	+–++	+	+	0	0
Ventral horn	+	+	+	+	0	0

Peckys & Landwehrmeyer, 1999

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  - enkephalins
    - major peptides: met-enkephalin & leu-enkephalin
    - precursor: proenkephalin
  - dynorphins
    - major peptides: dynorphin A, dynorphin B & neoendorphin
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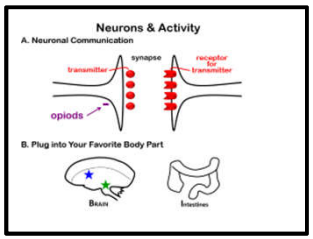
    - precursor: prodynorphin

Receptors

- 3 receptor types (all GPCRs):
  - μ (MOR)
    - Opens potassium channels
    - Closes calcium channels
    - Inhibits cAMP
- Widely distributed in the CNS
  - Not surprising considering profound effects opioids have on CNS function



Opioids & Receptors

Endogenous Opioid Analgesics

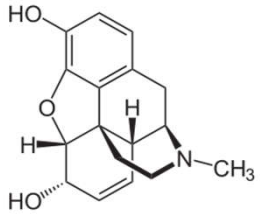
Opioid	Receptor		
	μ	δ	κ
β-endorphin	+++	+++	
met-enkephalin	++	+++	
leu-enkephalin	++	+++	
dynorphin A	++		+++
dynorphin B	+		+++

Opioids & Receptors

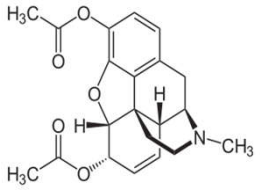
Common Opioid Analgesics

Opioid	Receptor		
	μ	δ	κ
Morphine	+++		+
Hydromorphone	+++		
Oxymorphone	+++		
Methadone	+++		
Meperidine	+++		
Fentanyl	+++		
Sufentanil	+++	+	+
Alfentanil	+++		
Remifentanil	+++		
Levorphanol	+++		
Codeine	+/-		
Hydrocodone	+/-		
Oxycodone	++		
Pentazocine	+/-		+
Nalbuphine	--		++
Buprenorphine	+/-	--	--
Butorphanol	+/-		+++

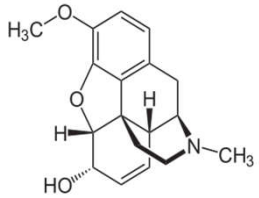
Morphine



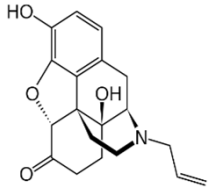
morphine



heroin



codeine



naltrexone

Summary

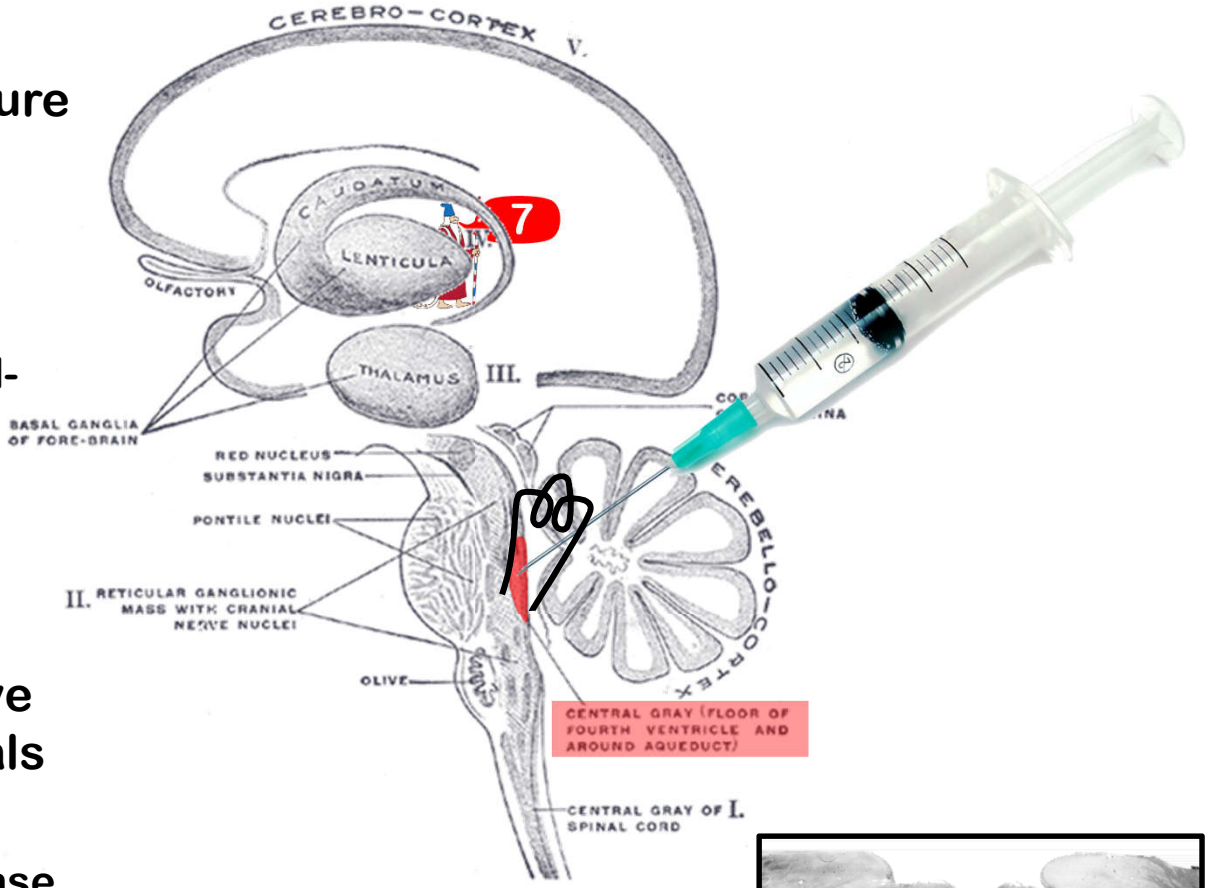
- Decreases pain but highly addictive (addiction potential similar to that of heroin)
- μ (MOR) – target of most opiate analgesics
- MORs expressed in the periaqueductal gray (PAG)
- MORs expressed in the spinal cord

"The analgesic actions of opiates after systemic delivery are believed to represent actions in the brain, spinal cord, & in some instances in the periphery."

- Goodman & Gilman

Periaqueductal Gray (PAG)

- mesencephalic structure
- projects to rostral ventromedial medulla
  - constitutes essential neural circuit for opioid-based analgesia
- high density of MORs
- administration of opioids directly into PAG blocks nociceptive responses in all animals (rodents to primates)
  - naloxone blocks response
- direct electrical stimulation of PAG produces analgesia



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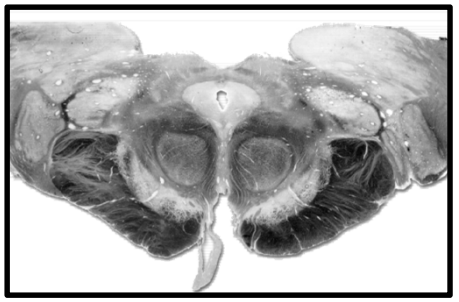
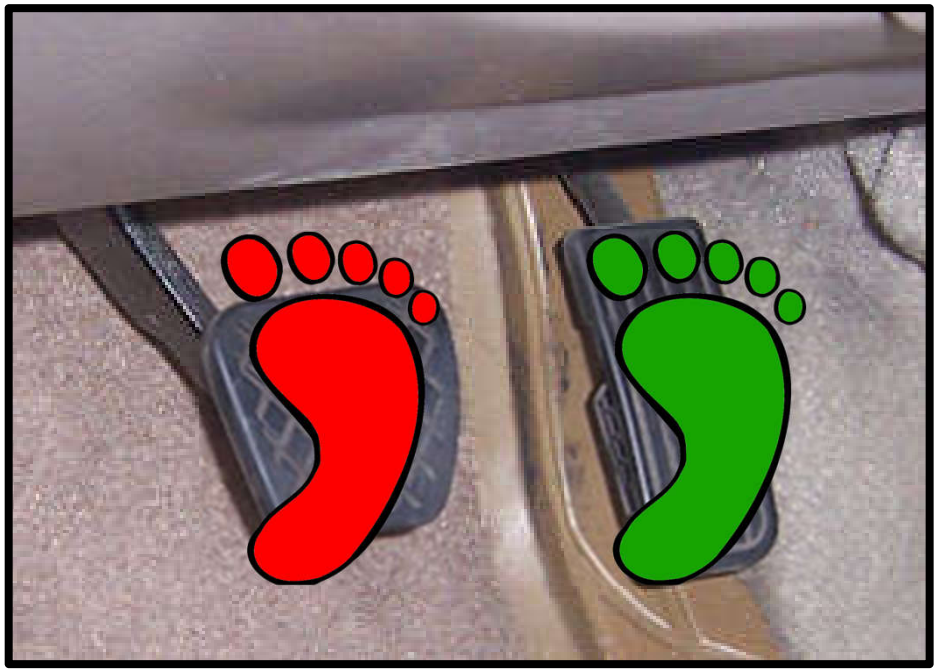


Mechanisms of Opiate Analgesia



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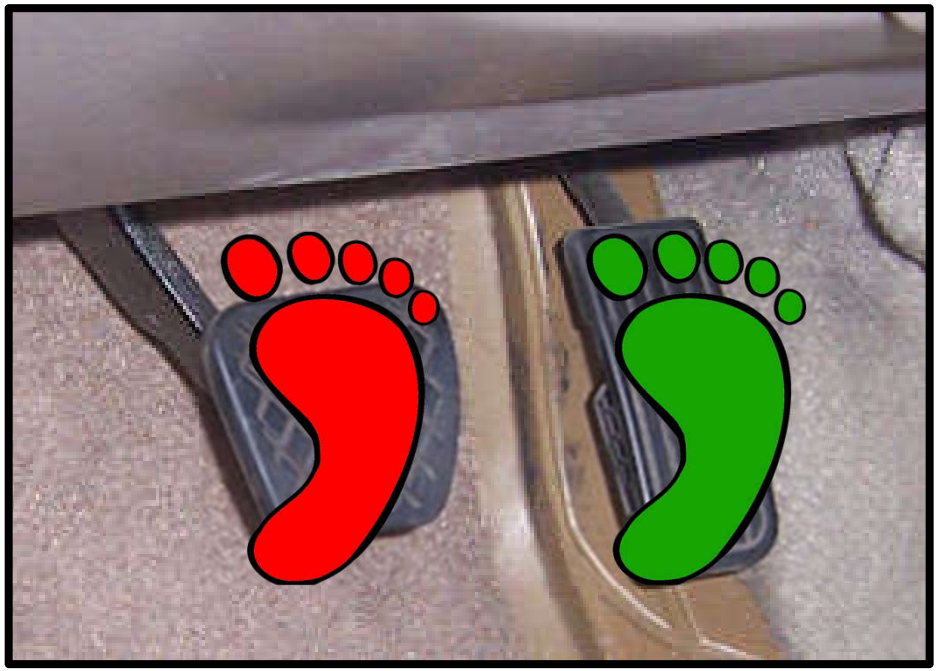


But What's the Point?

Sometimes You're Already to Go, but Something's Stopping You

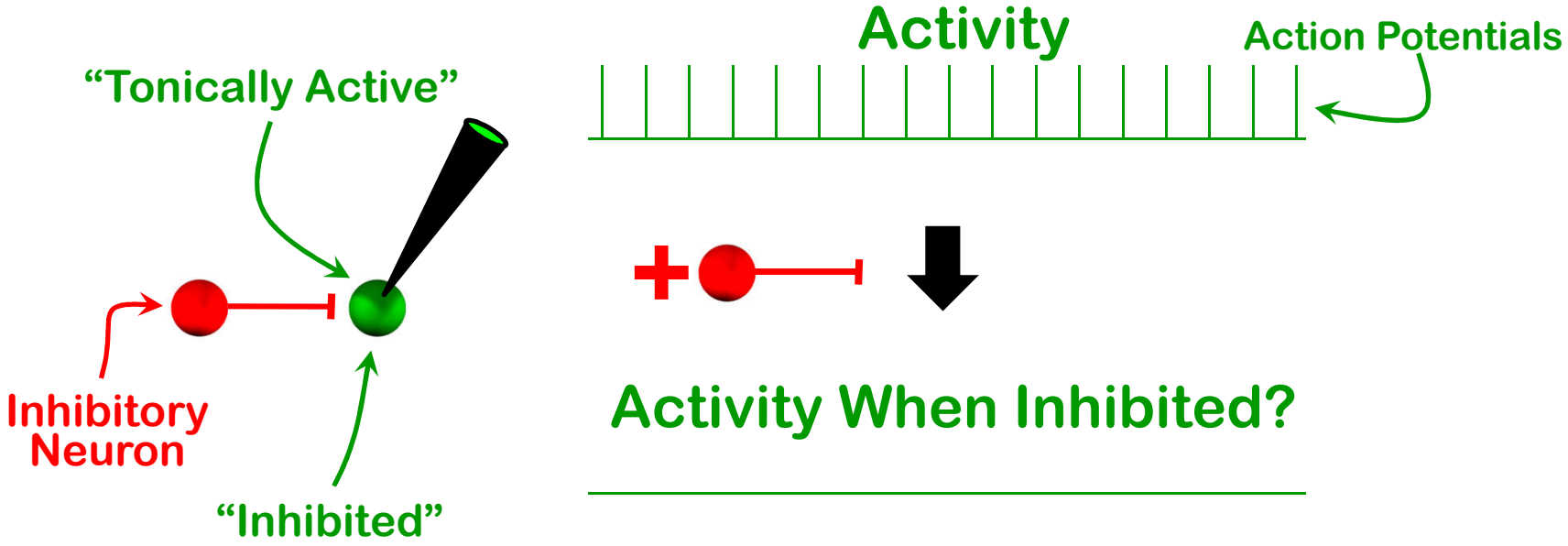
Mechanisms of Opiate Analgesia

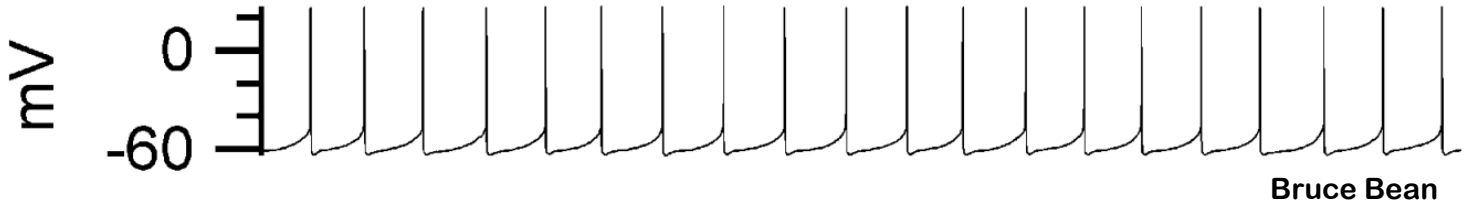
<u>But What's the Point?</u>

Sometimes You're Already to Go, but Something's Stopping You

Mechanisms of Opiate Analgesia

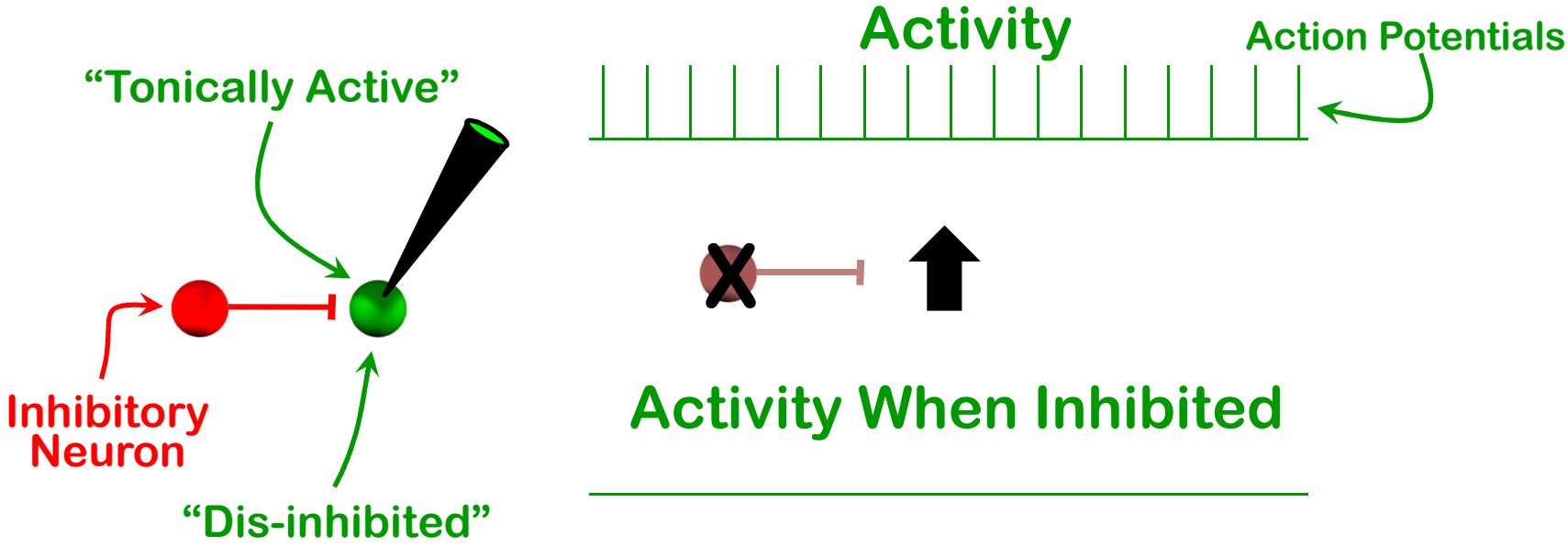
Scenario #1

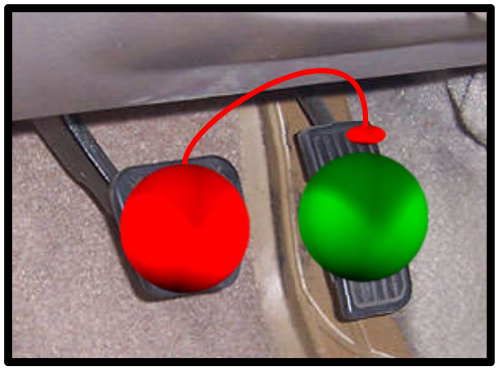




Mechanisms of Opiate Analgesia

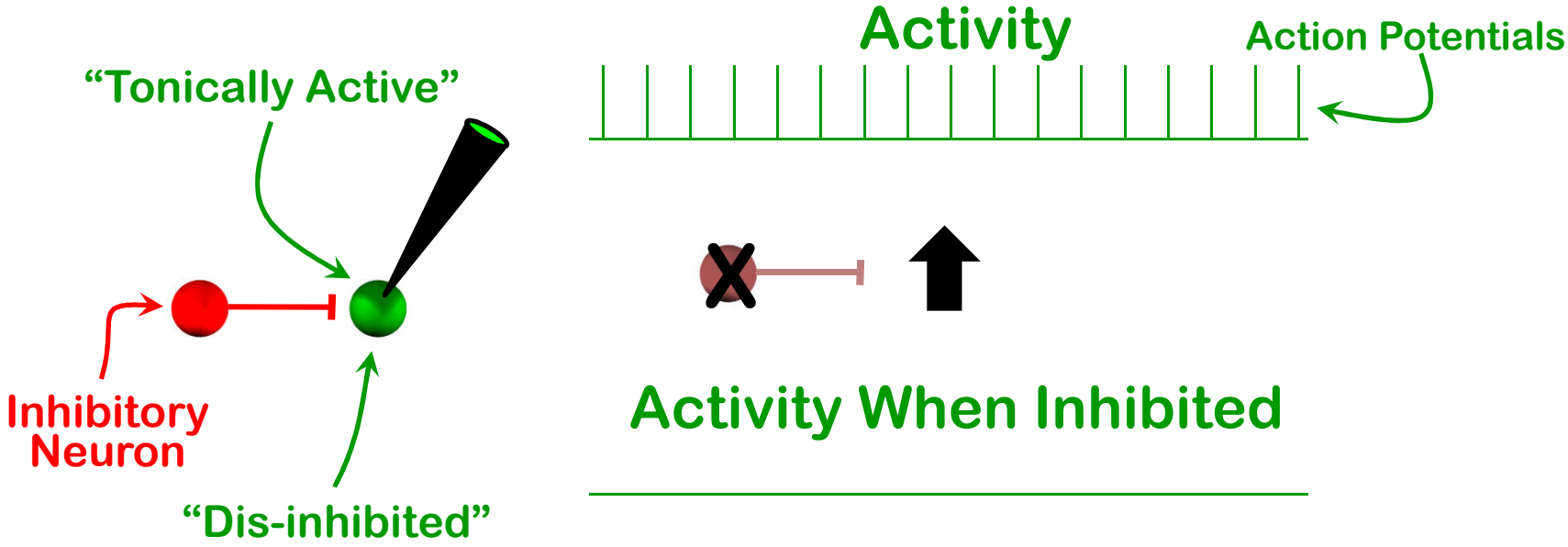
Scenario #2



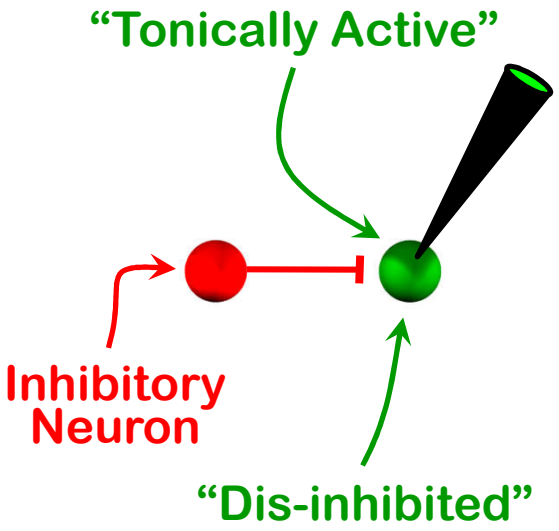


Mechanisms of Opiate Analgesia

Scenario #2



Mechanisms of Opiate Analgesia



Scenario #2

But what's the point?

Neurons Do Not Require Synaptic Excitation to Turn On

Removal of Inhibition (Dis-inhibition) Can Also Turn Neurons On

Periaqueductal Gray (PAG)

- mesencephalic structure
- projects to rostral ventromedial medulla
  - constitutes essential neural circuit for opioid-based analgesia
- high density of MORs
- administration of opioids directly into PAG blocks nociceptive responses in all animals (rodents to primates)
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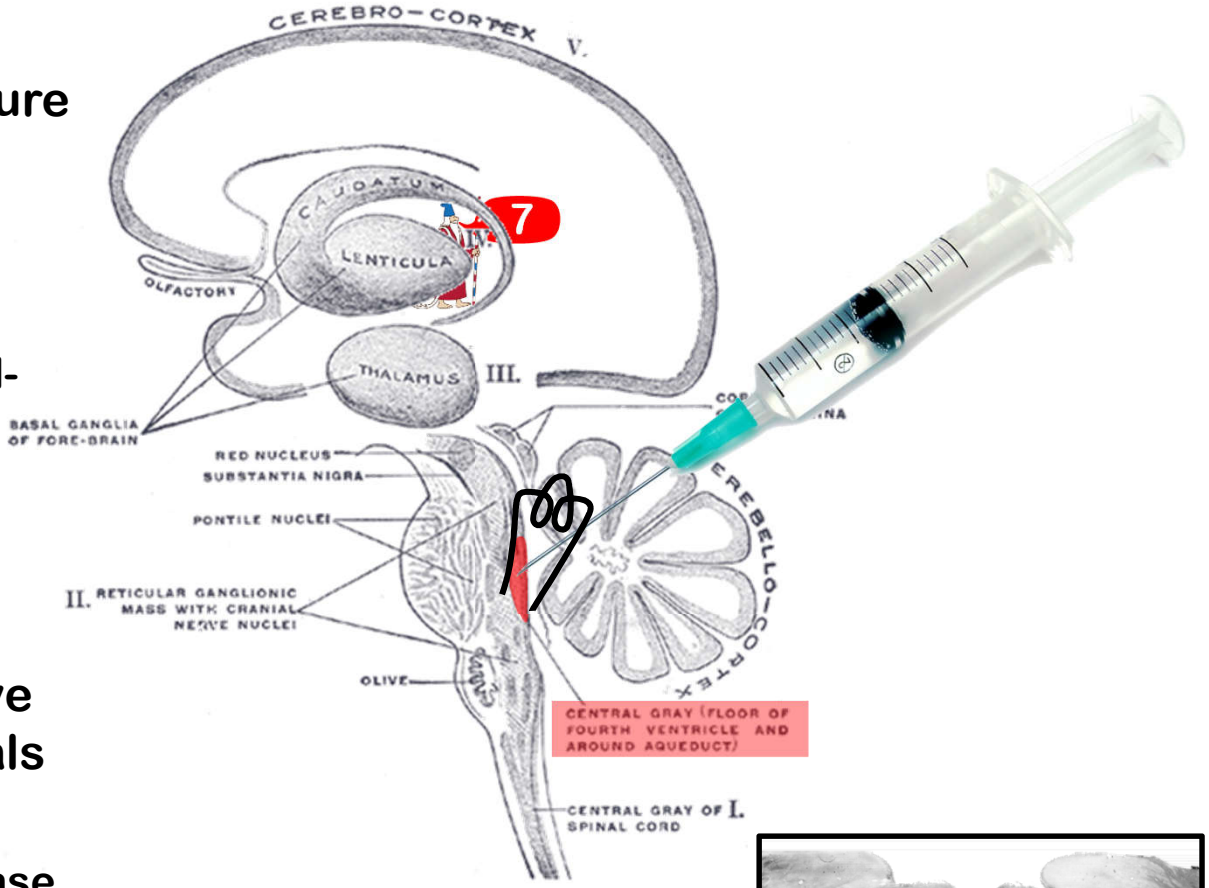
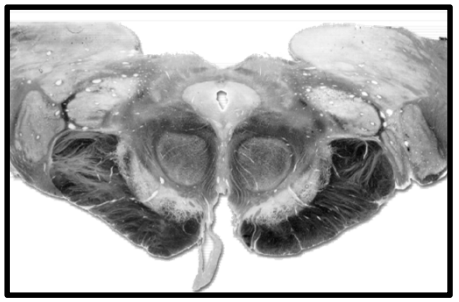
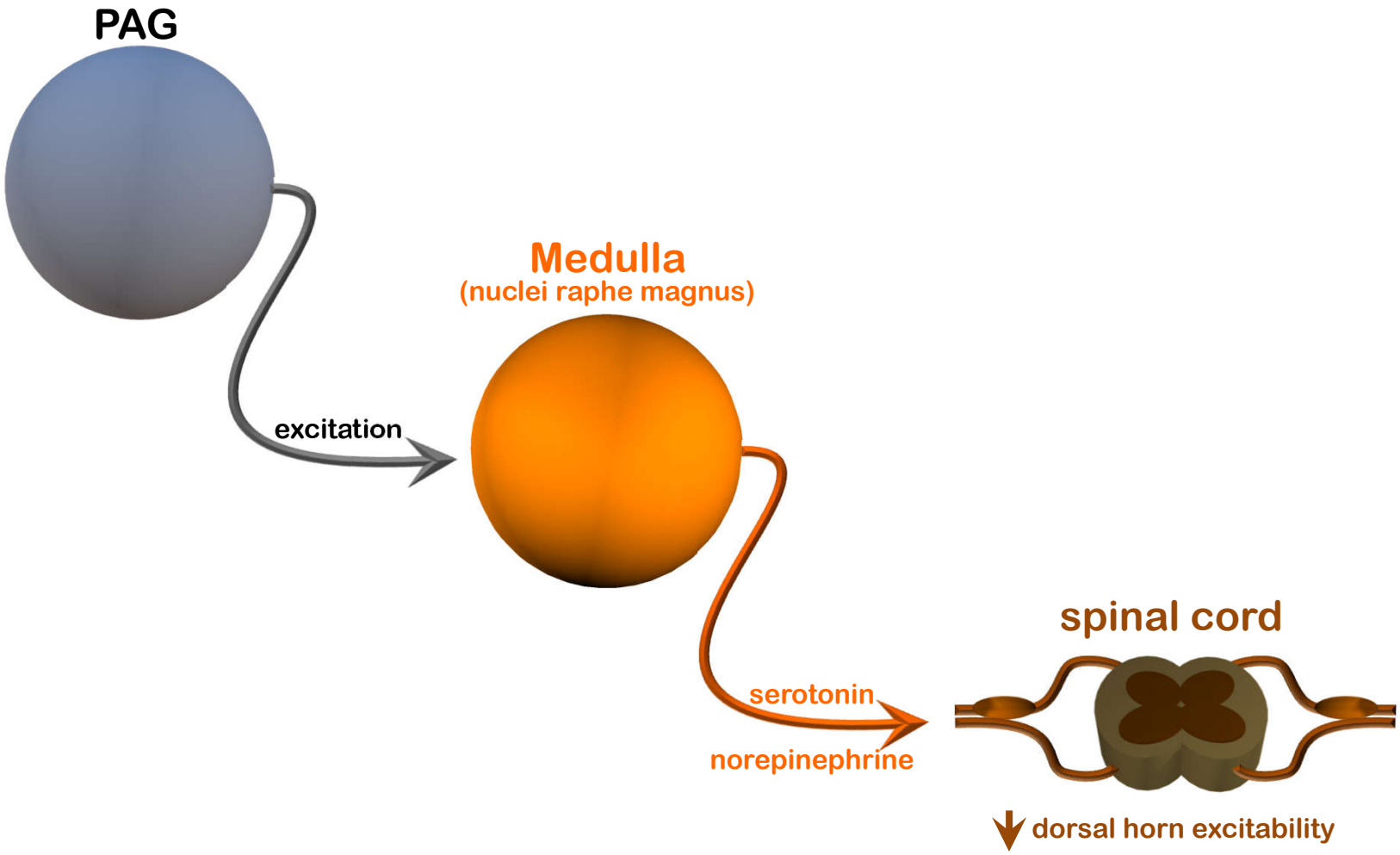


wikipedia

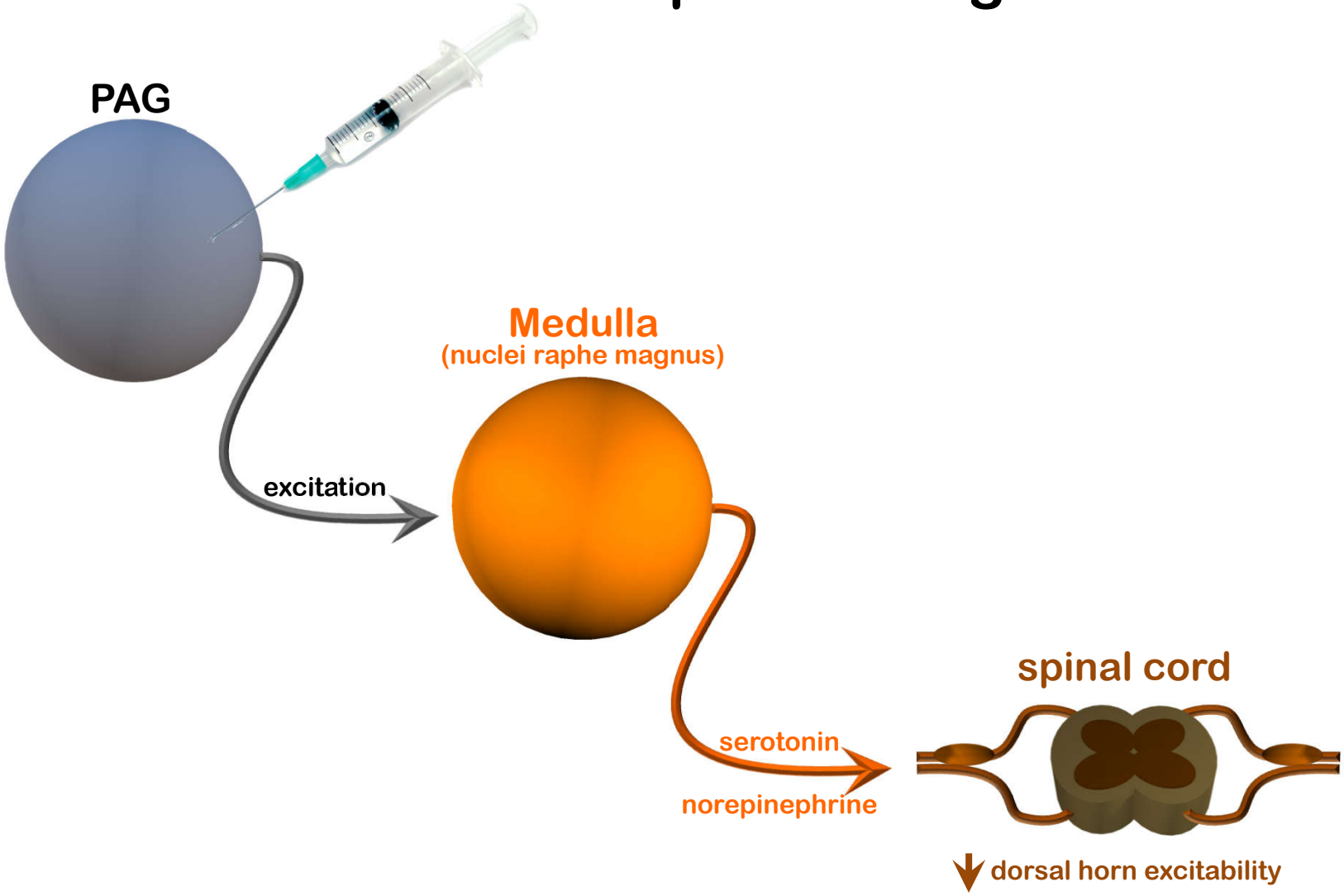


Mechanisms of Opiate Analgesia

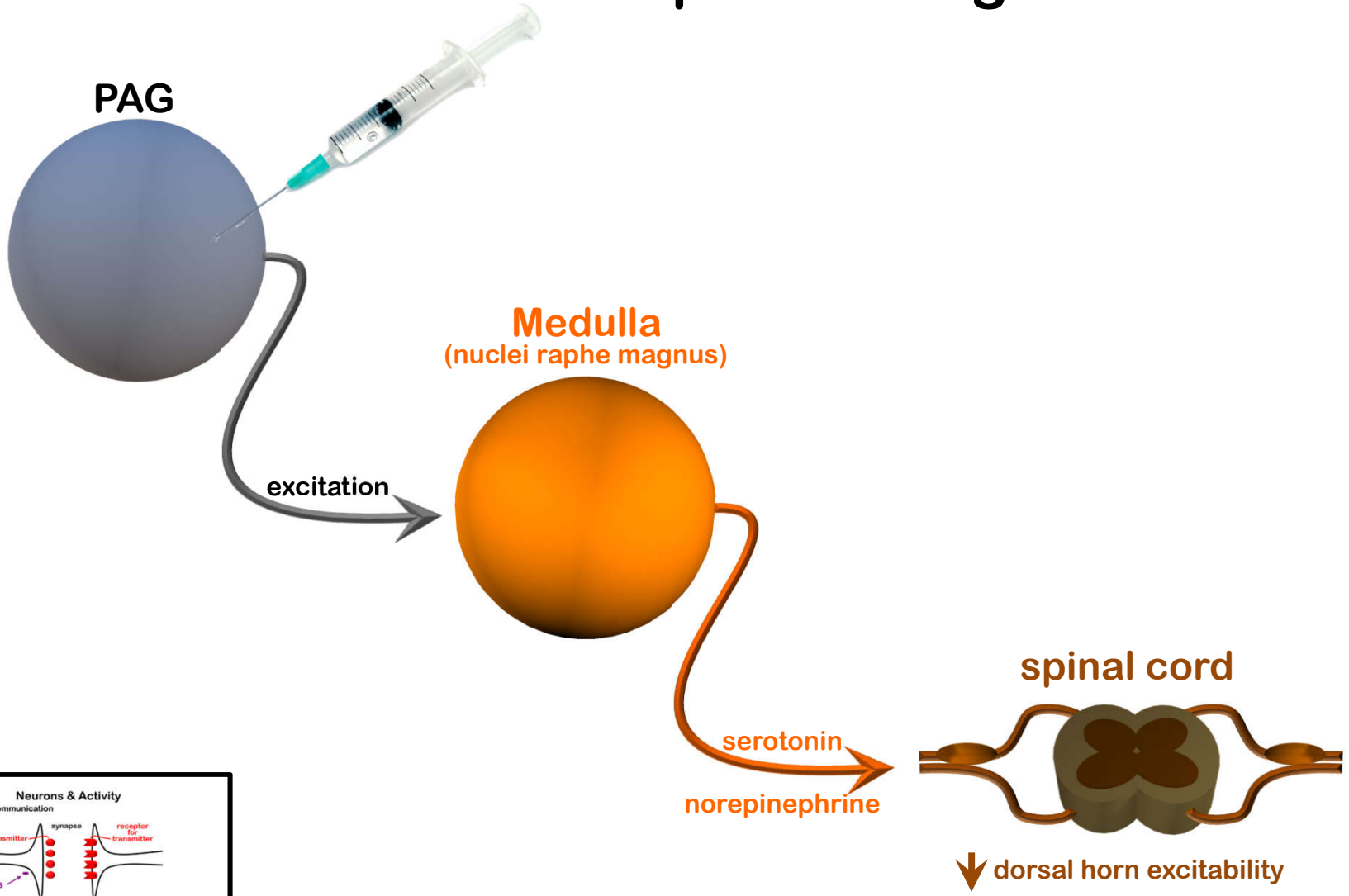


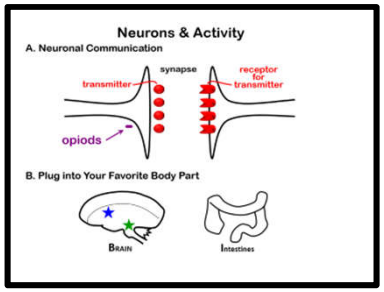
Neuroscience Online: UT Health Center

Mechanisms of Opiate Analgesia



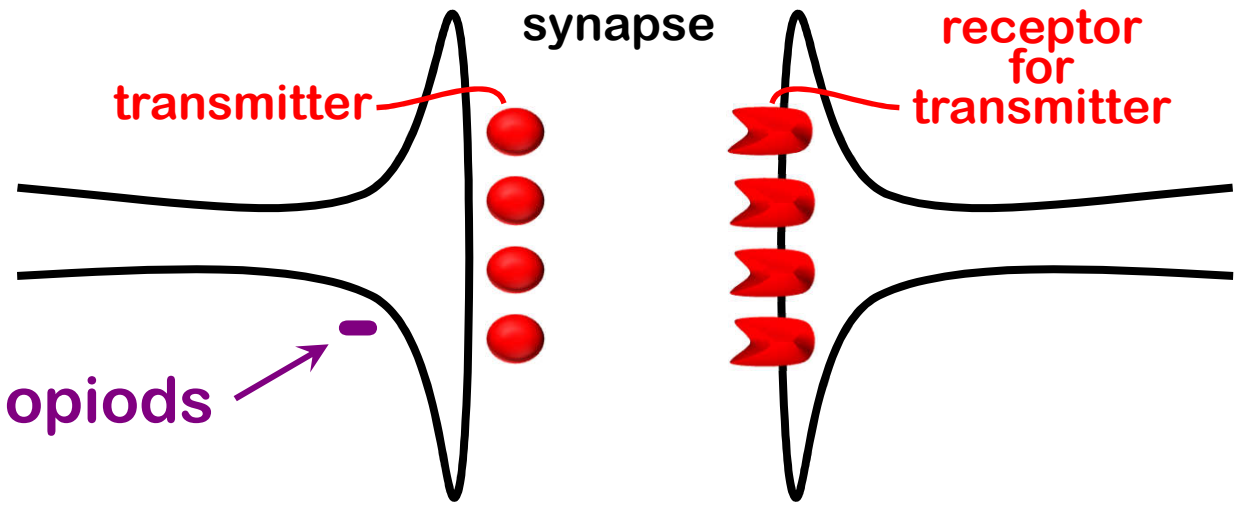
Mechanisms of Opiate Analgesia



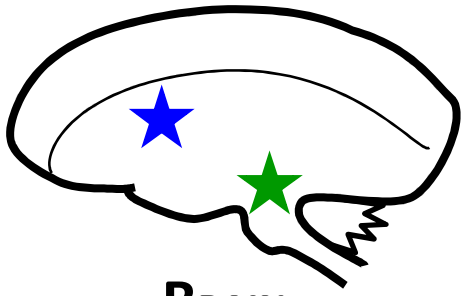


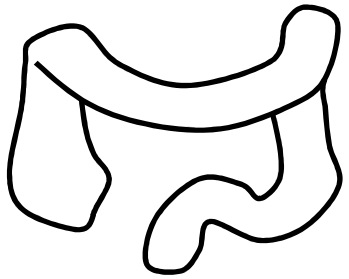
Neurons & Activity

A. Neuronal Communication

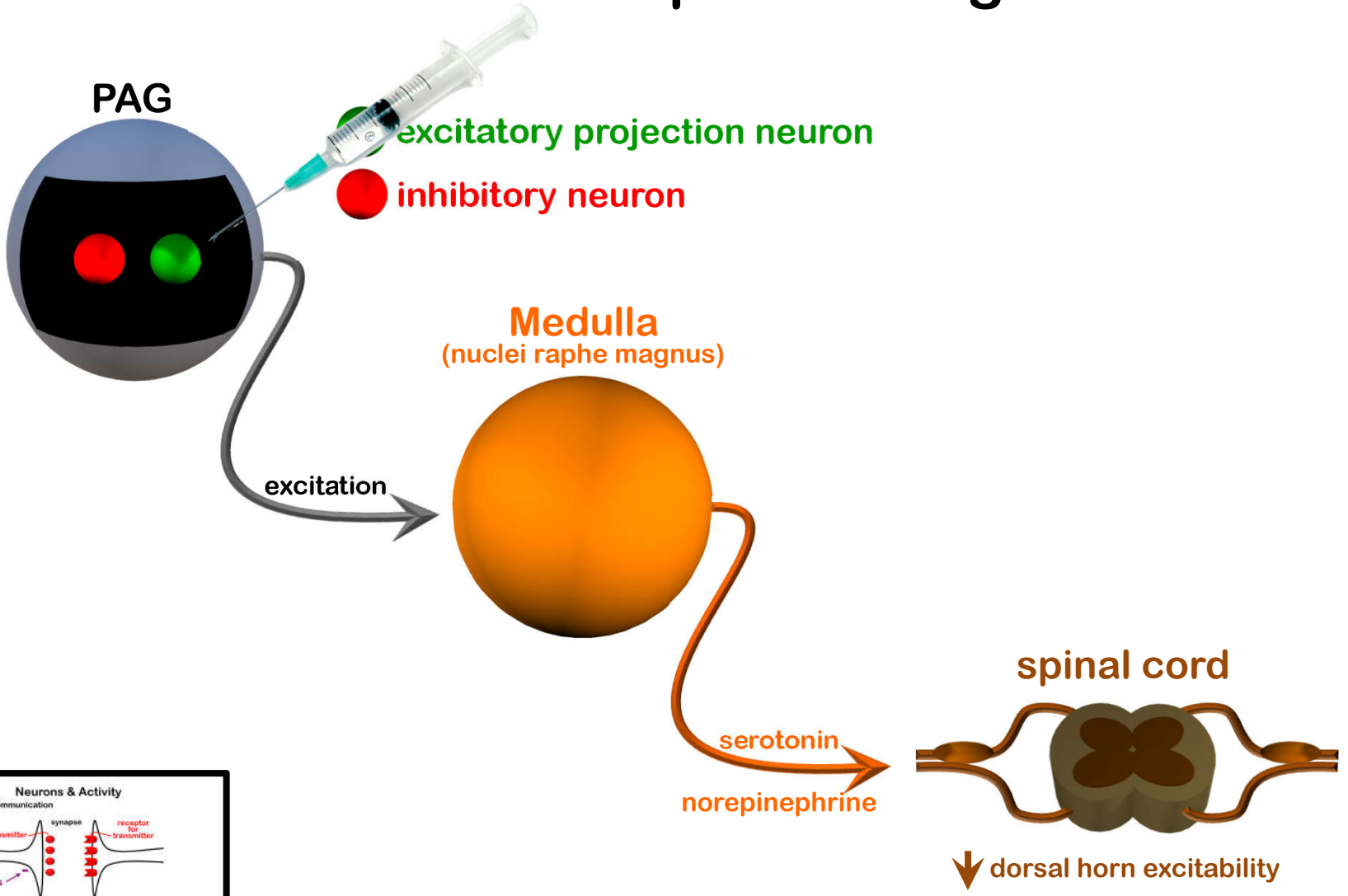


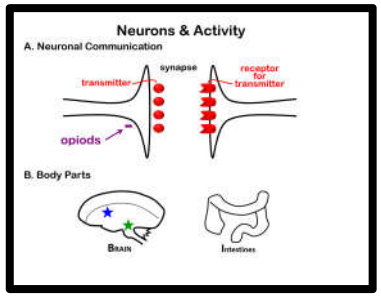
B. Plug into Your Favorite Body Part





Mechanisms of Opiate Analgesia





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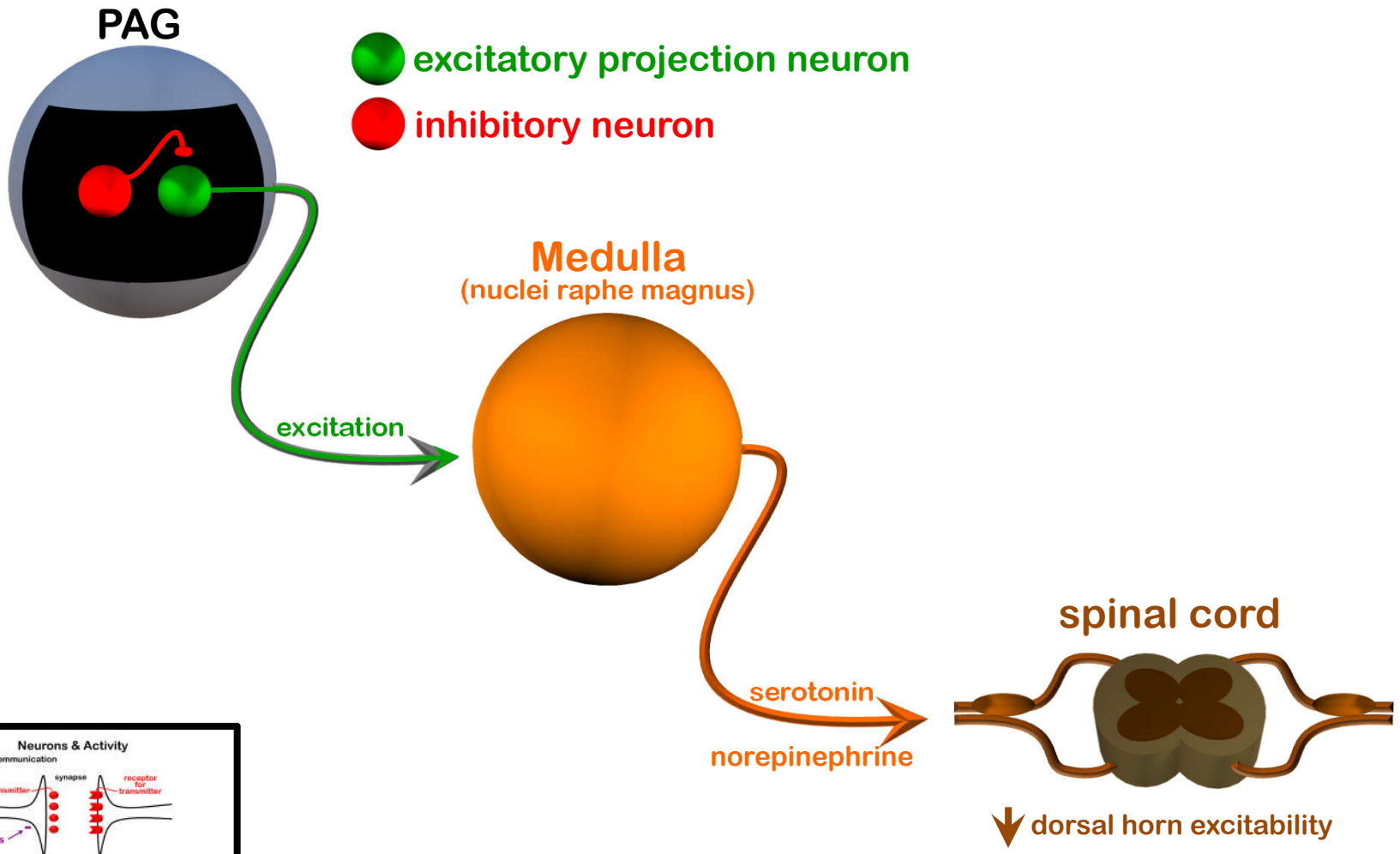

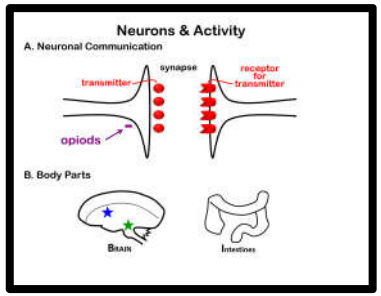

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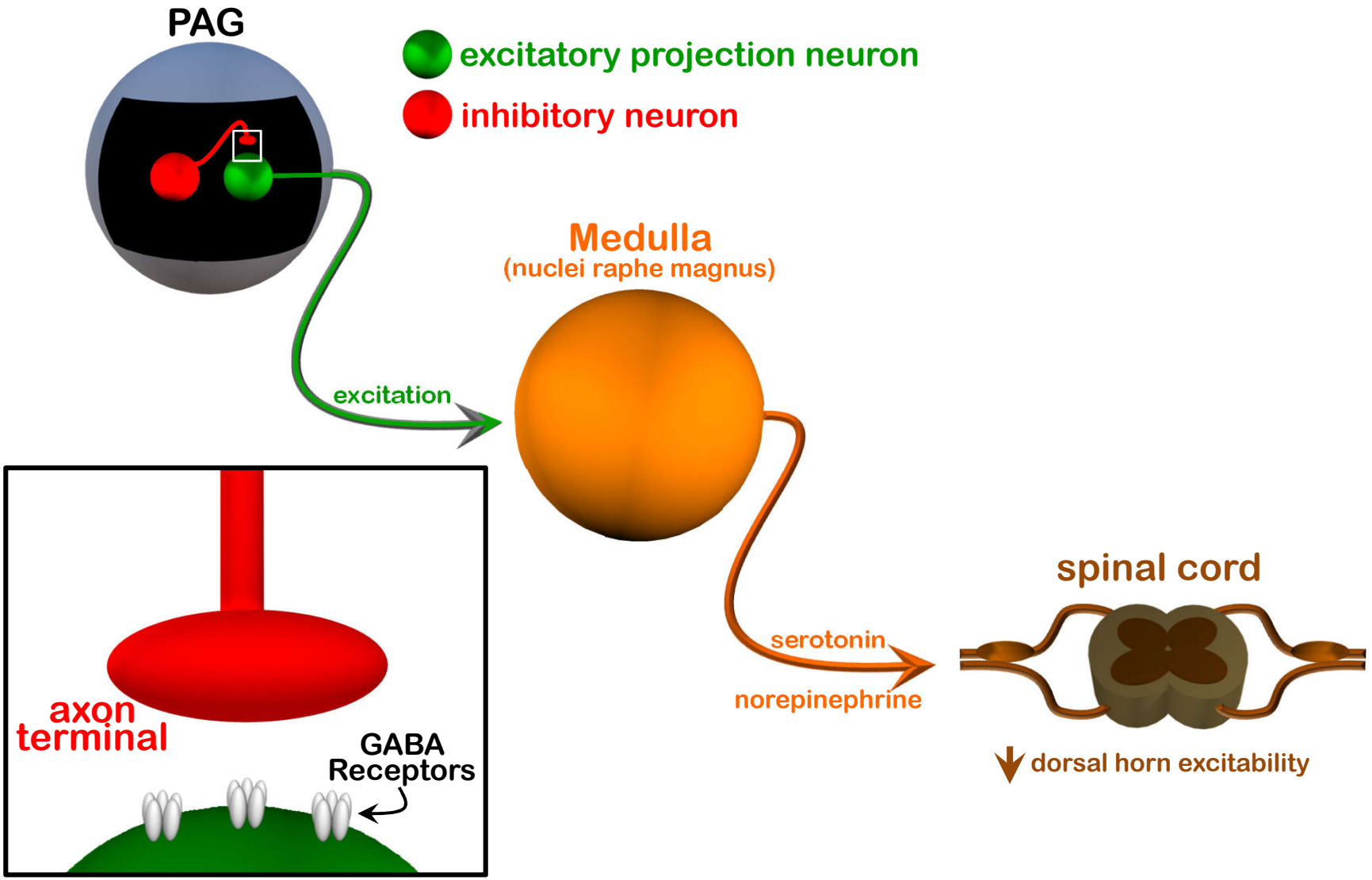

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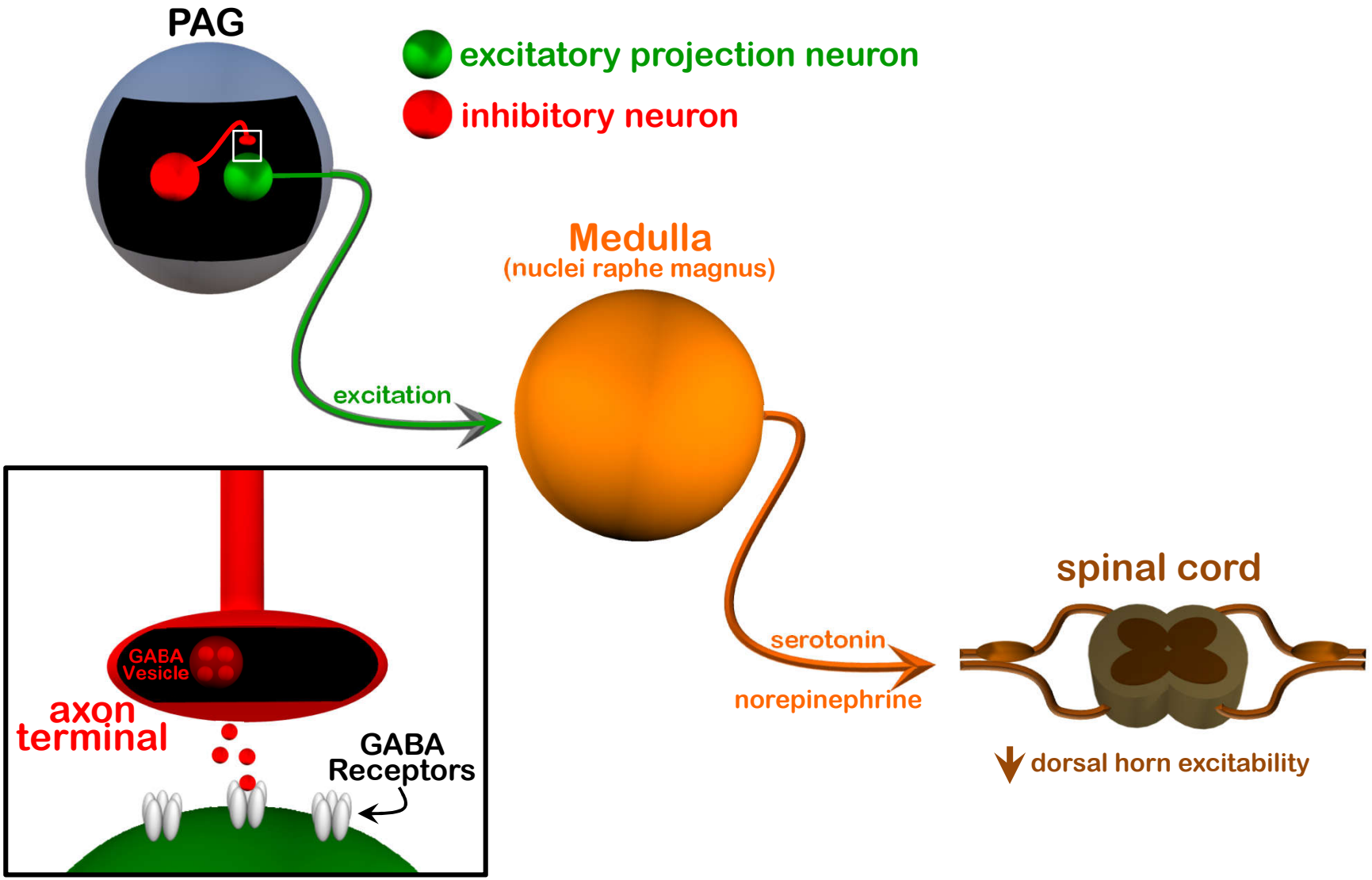

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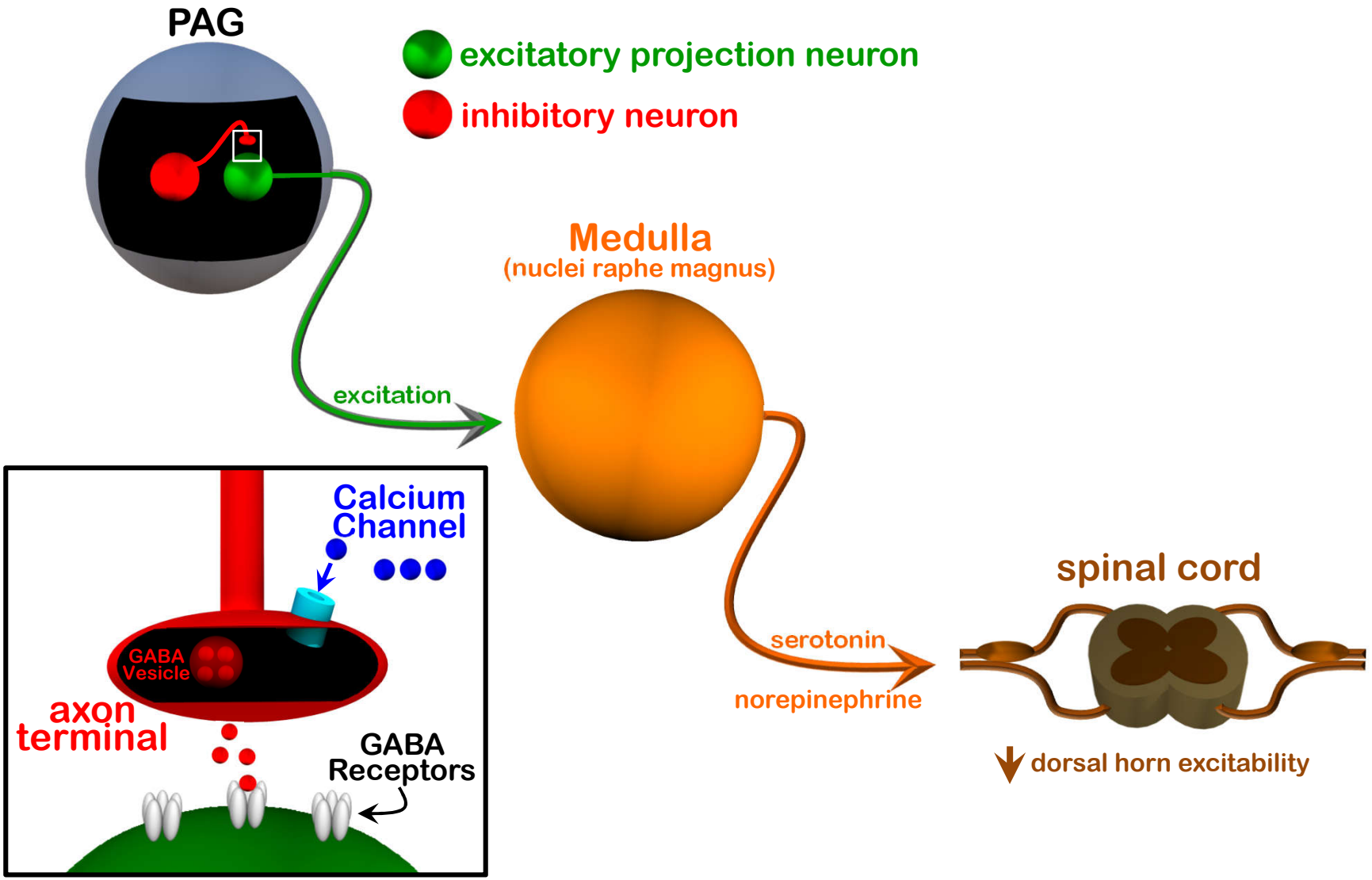
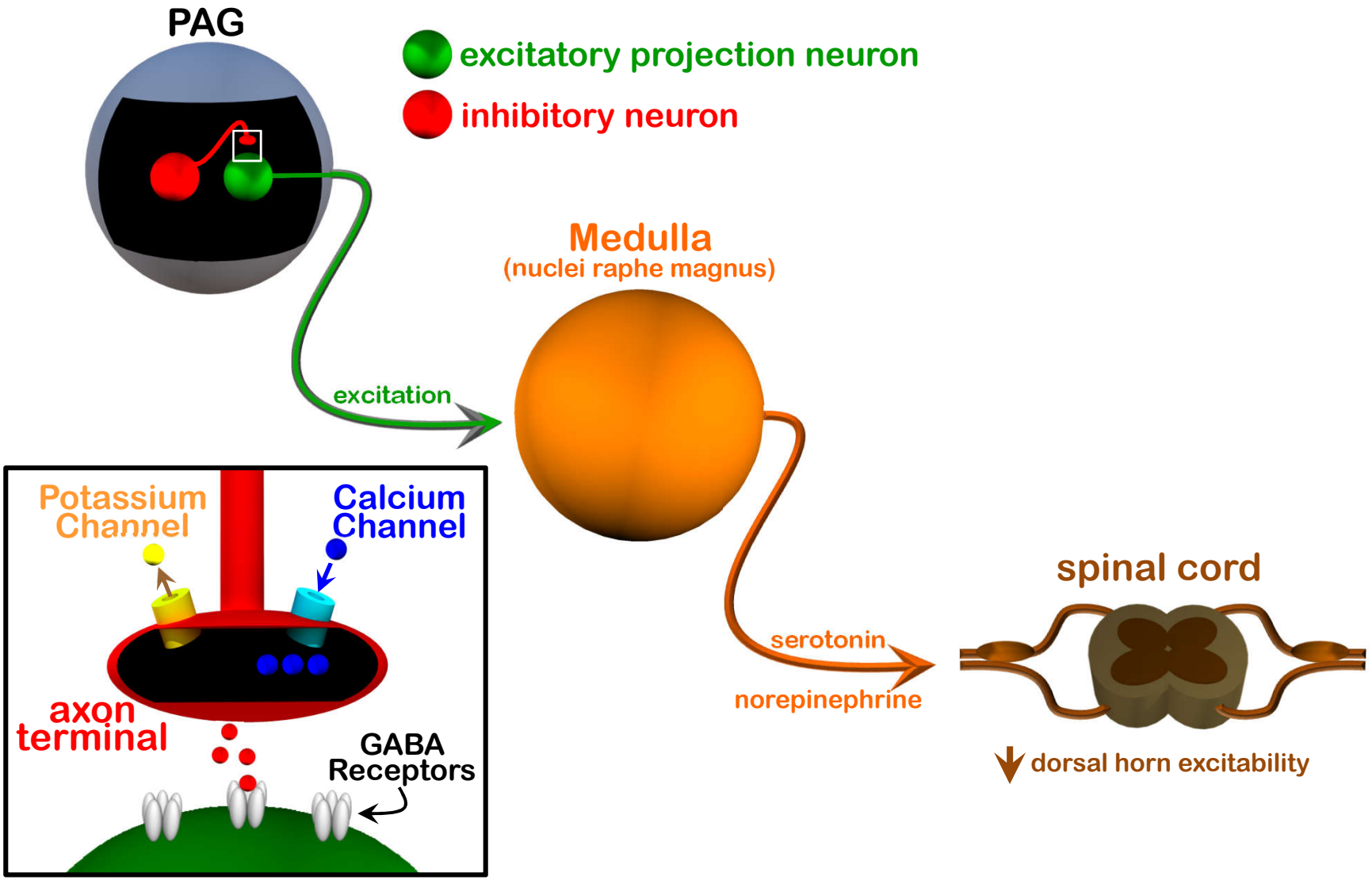


Mechanisms of Opiate Analgesia



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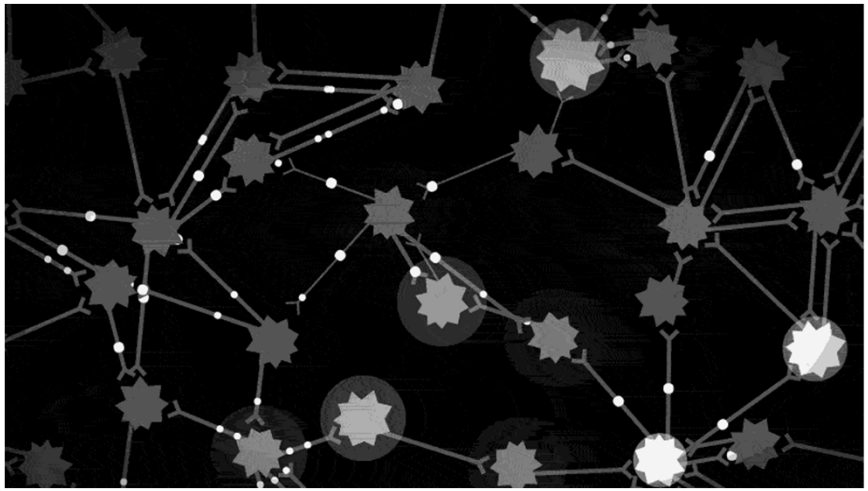
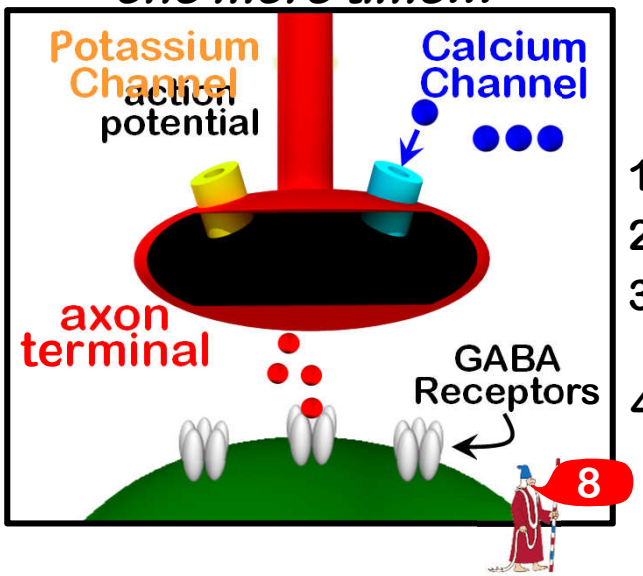
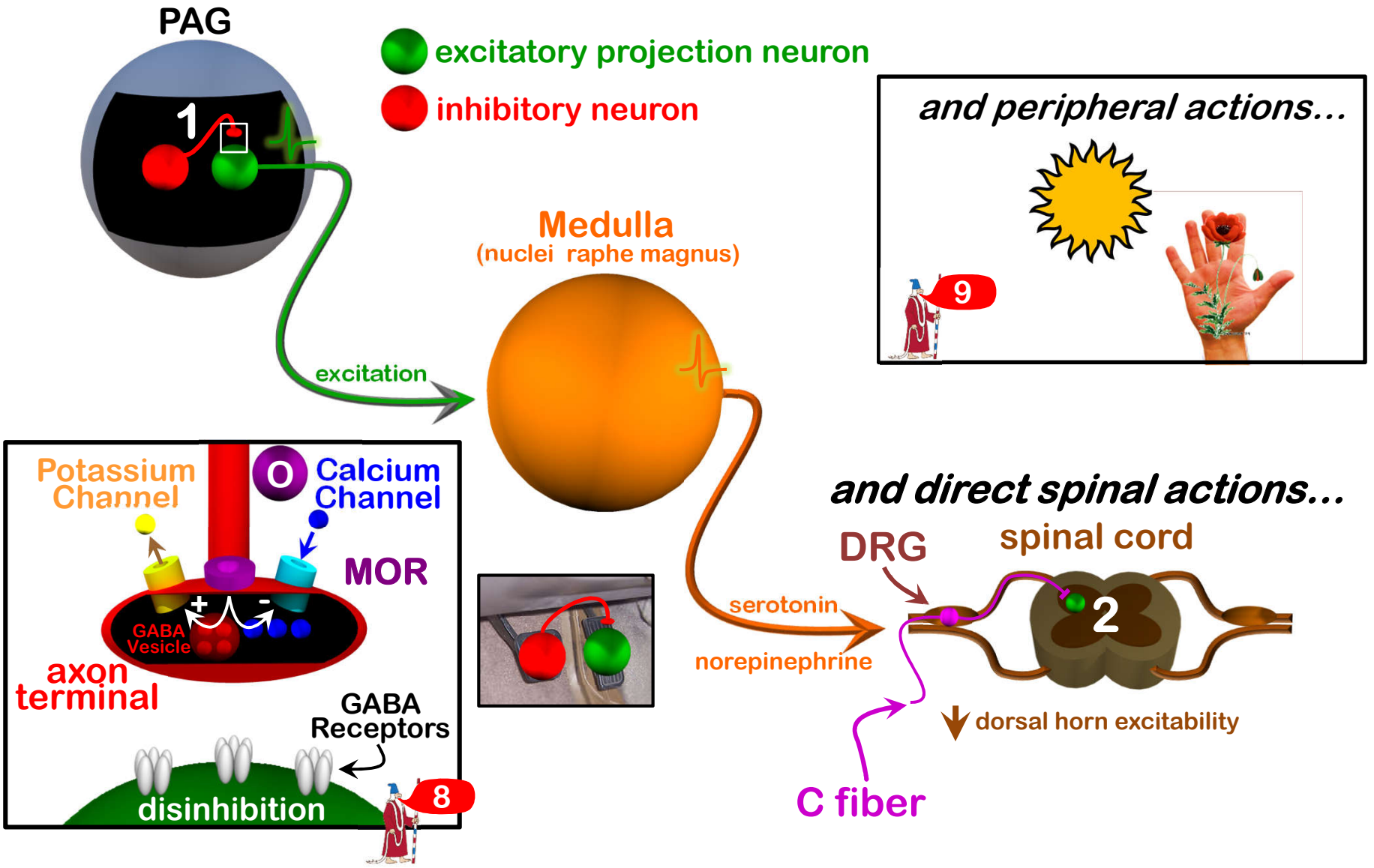


one more time…



1) Positive change in voltage opens calcium channels
2) Calcium influx triggers vesicle release
3) Opening potassium channels causes negative change in voltage
4) Negative change in voltage: calcium channels *less* likely to open.

Mechanisms of Opiate Analgesia



Opioids & Receptors

Common Opioid Analgesics

Opioid	Receptor μ	δ	κ
Morphine	+++		+
Hydromorphone	+++		
Oxymorphone	+++		
Methadone	+++		
Meperidine	+++	Strong Agonists	
Fentanyl	+++		
Sufentanil	+++	+	+
Alfentanil	+++		
Remifentanil	+++		
Levorphanol	+++		
Codeine	+/-		
Hydrocodone	+	Mild to Moderate Agonists	
Oxycodone	++		
Pentazocine	+/-		+
Nalbuphine	--	Mixed Actions	++
Buprenorphine	+/-	--	--
Butorphanol	+/-		+++

Opioids & Receptors

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Opioid

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Buprenorphine
Butorphanol

Lange, 12th Edition

Physiological Effects of Morphine

- **CNS Effects**
  - **Analgesia**
    - both sensory & emotional components
  - **Euphoria**
  - **Sedation**
    - more common in the elderly
    - more common with the phenanthrenes (codeine, hydrocodone)
  - **Respiratory Depression**
    - all opioid analgesics produce significant respiratory depression by inhibiting brainstem respiratory mechanisms
    - dose-dependent
  - **Cough Suppression**
    - codeine
    - supresses cough reflex
  - **Miosis**
    - valuable for diagnosing overdose
  - **Truncal Rigidity**
  - **Nausea & Vomiting**
  - **Temperature**
    - opioids can produce either hyperthermia (MOR agonists) or hypothermia (KOR agonists)

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Physiological Effects of Morphine

M **RAT SCENT**

Physiological Effects of Morphine

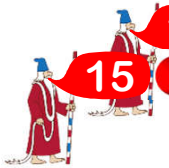
- **Peripheral Effects**
  - **Gastrointestinal**
    - constipation
    - tolerance does not develop (i.e. effect does not diminish)
  - **Biliary Tract**
    - opioids contract biliary smooth muscle
    - can cause biliary colic
  - **Renal**
    - opioids depress renal function
  - **Uterus**
    - opioids may prolong labor

Clinical Uses of Morphine

- **Clinical Use**
  - **Analgesia**
    - severe, constant pain usually relieved
    - sharp, intermittent pain less effectively controlled
  - **Acute Pulmonary Edema**
    - historically used to relieve dyspnea associated with pulmonary edema
    - HOWEVER, recent studies find little evidence in support of this use
  - **Cough**
    - Low dose oral morphine can significantly suppress chronic cough but side effect profile may limit widespread utility
    - Codeine & dextramethorphan: commonly prescribed antitussives
      - Recent studies suggest that these have little/no efficacy relative to placebo in humans with chronic cough
  - **Diarrhea**
  - **Shivering**

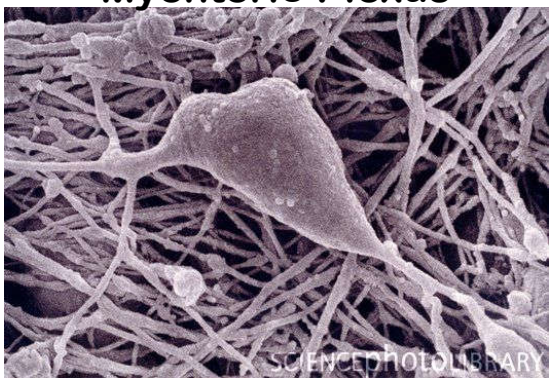
Side Effects of Morphine

- **Respiratory depression**
  - Respiration rate is decreased
  - Affects respiratory centers (medulla oblongata & pons)
    - morphine reduces CO_2-dependent activation of respiratory centers
  - Dose threshold for analgesic & respiratory effects are the same
  - Lethal effects of morphine due to respiratory arrest, hypoxia & cardiovascular collapse



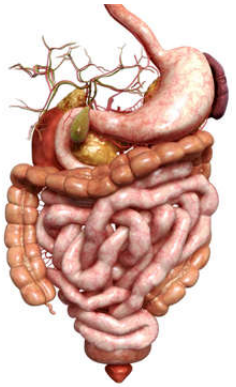
- **Decreased gut motility (i.e. constipation)**
  - Inhibits output of the myenteric plexus (also called “Auerbach’s” plexus)
    - Reduces propulsive contractions of longitudinal muscles

Myenteric Plexus



Acetylcholine

GI Tract



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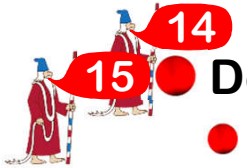

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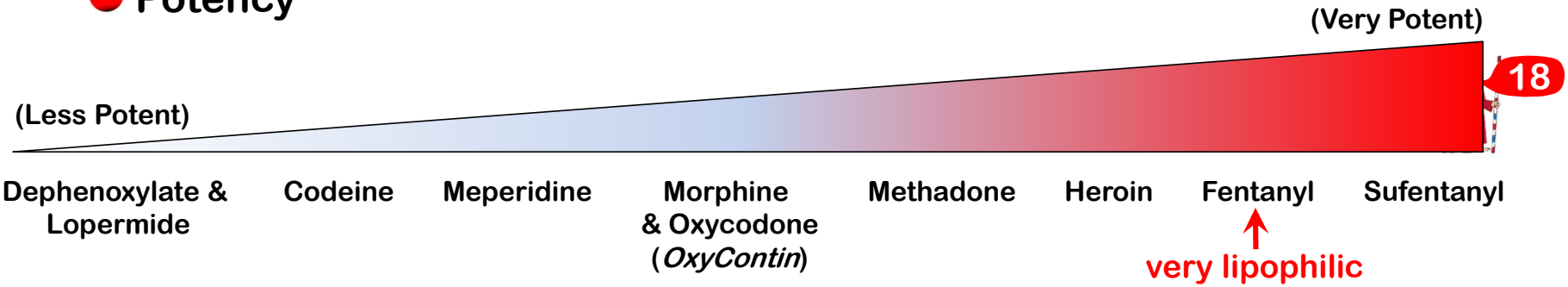
    - Reduces propulsive contractions of longitudinal muscles

- **Difficulty with urination**
  - Inhibits urinary voiding reflex
  - Catheterization may be required after therapeutic doses of morphine

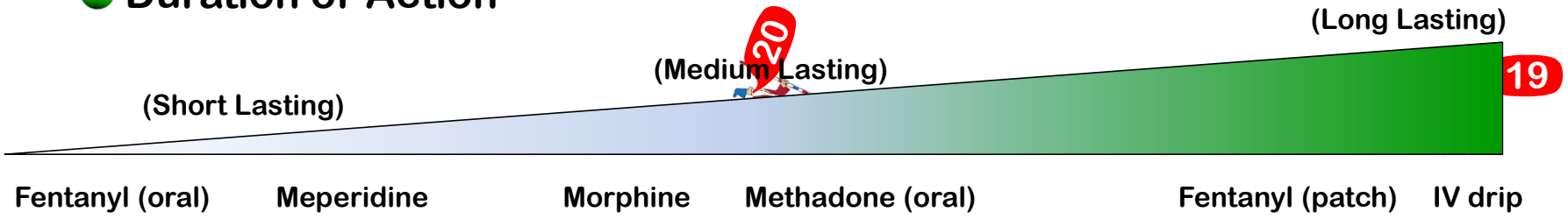
- **May cause orthostatic hypotension**
  - Morphine is a powerful depressant of the medullary vasomotor center
  - Has relatively little effect on blood pressure when recumbant
  - Can produce severe hypotension in patient who has lost blood
- **Allergic reaction**

Differences Among the Major Opiates

Potency



Duration of Action

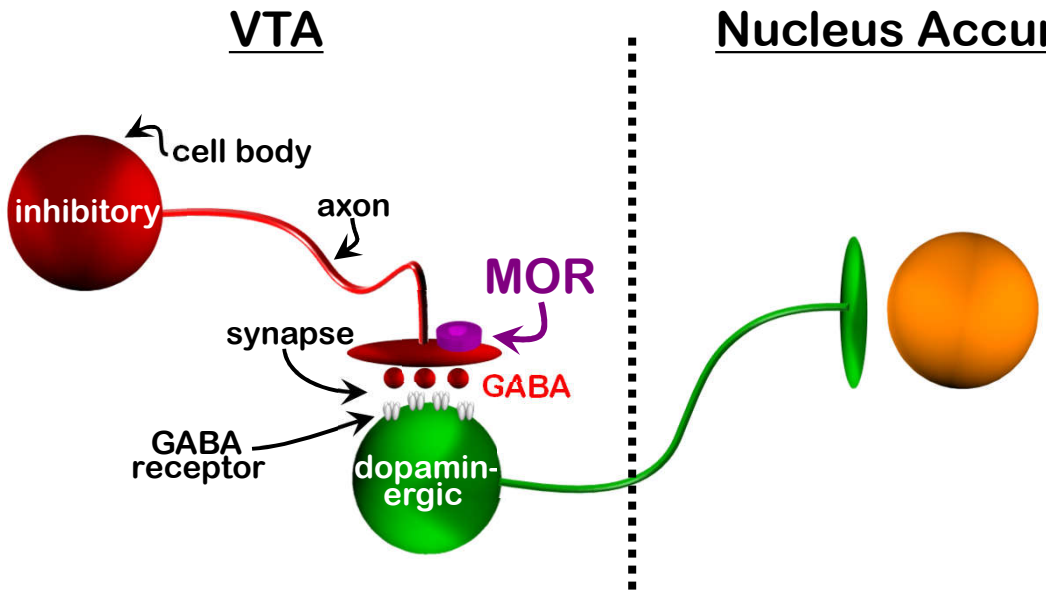


Partial MOR agonists: Pentazocine & Buprenorphine

- Used to treat pain
- Less respiratory depression
  - Can antagonize respiratory depression produced by Fentanyl without completely reversing pain (Buprenorphine)
- But can cause hallucinations/nightmares (Pentazocine)

Opiate Abuse

- Opiates have powerful effect on reward pathway
- Mechanism: increase dopamine release from the ventral tegmental area (VTA)



- Treatment
  - Medically supervised withdrawal alone is often insufficient to prevent relapse
  - Withdrawal symptoms:
    - Dysphoria, anxiety, restlessness, insomnia
    - High blood pressure, tachycardia, diarrhea

Opiate Overdose

- **Symptoms**
  - Very low respiratory rate
  - Hypotension
  - Hypothermia
  - Pin-point pupils (except when hypoxia becomes severe)
  - Coma

- **Treatment**
  - Ventilation
  - Naloxone (repeated, small IV doses)
    - Opiate receptor antagonist (MOR)…or an inverse agonist?
    - Reverses all effects except whose due to prolonged hypoxia
    - Has very little oral bio-availability
    - Short T1/2
    - Naltrexone Comparison. Naltrexone:
      - Longer T1/2
      - Can be taken orally
      - Primarily used for long-term treatment of opioid addiction
    - Nalmefene Comparison. Nalmefene:
      - Longer T1/2
      - Can be taken orally
      - Expensive
      - More universal antagonist: MOR, KOR, DOR
      - Primarily used for management of alcohol dependence

Opioid ~~Analgesics~~ Addiction

Young Victims of the Opioid Epidemic

By THE EDITORIAL BOARD JAN. 16, 2017

Lilli Carré

New York Times, January 2017

Opioid ~~Analgesics~~
Addiction

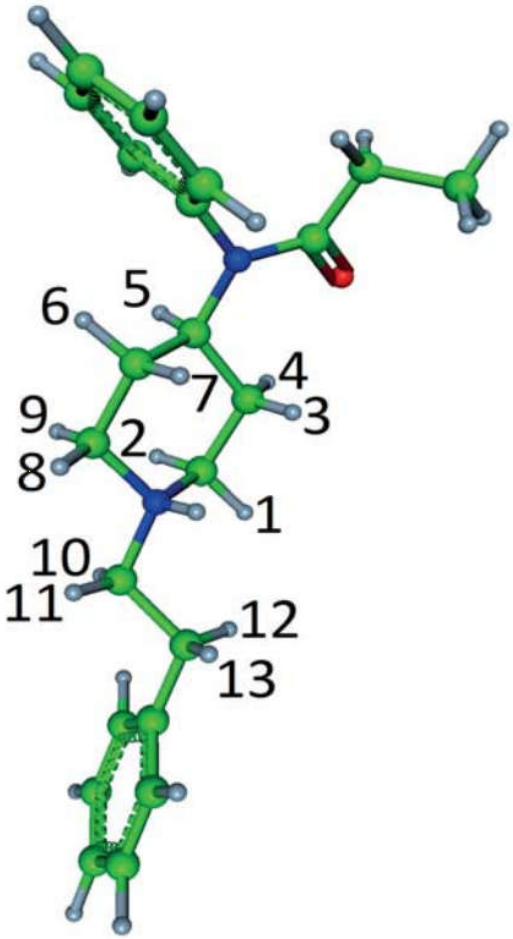
REPORT

PAIN RESEARCH

A nontoxic pain killer designed by modeling of pathological receptor conformations

V. Spahn,[1]† G. Del Vecchio,[1]† D. Labuz,[1] A. Rodriguez-Gaztelumendi,[1] N. Massaly,[1]*
J. Temp,[1] V. Durmaz,[2] P. Sabri,[2] M. Reidelbach,[2] H. Machelska,[1]
M. Weber,[2]‡ C. Stein[1]‡§

Indiscriminate activation of opioid receptors provides pain relief but also severe central and intestinal side effects. We hypothesized that exploiting pathological (rather than physiological) conformation dynamics of opioid receptor-ligand interactions might yield ligands without adverse actions. By computer simulations at low pH, a hallmark of injured tissue, we designed an agonist that, because of its low acid dissociation constant, selectively activates peripheral μ-opioid receptors at the source of pain generation. Unlike the conventional opioid fentanyl, this agonist showed pH-sensitive binding, heterotrimeric guanine nucleotide–binding protein (G protein) subunit dissociation by fluorescence resonance energy transfer, and adenosine 3′,5′-monophosphate inhibition in vitro. It produced injury-restricted analgesia in rats with different types of inflammatory pain without exhibiting respiratory depression, sedation, constipation, or addiction potential.



Quiz

- opiate-free

- taking opiates for pain
- never abused opiates

- dependent on opiates
- currently under the influence of opiates

Naloxone

Quiz

opiate-free

taking opiates for pain

never abused opiates

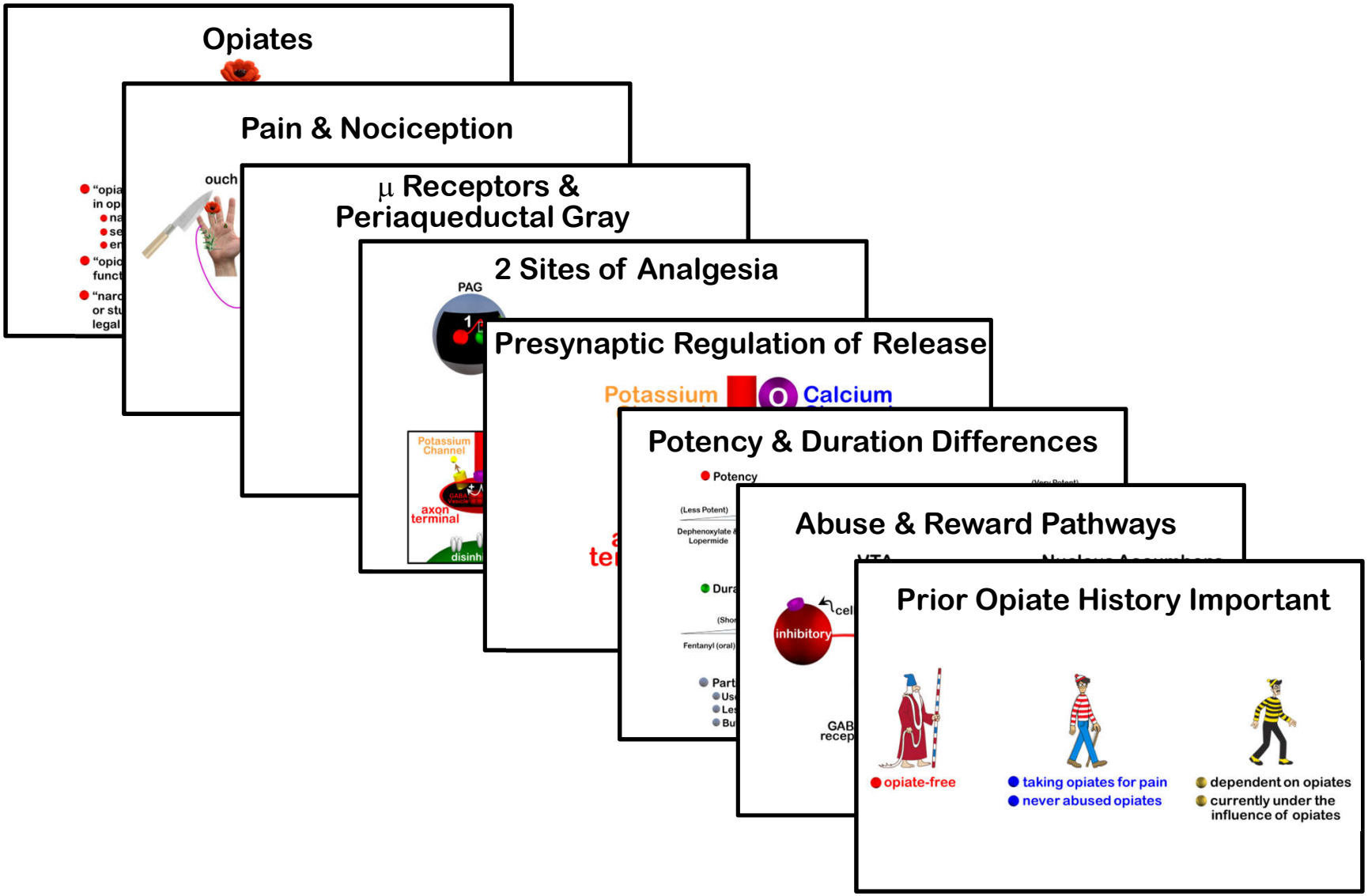
dependent on opiates

currently drug free

Naloxone

Buprenorphine

Summary


Opiates
Pain & Nociception
ouch
μ Receptors & Periaqueductal Gray
2 Sites of Analgesia
PAG
Presynaptic Regulation of Release
Potassium
Calcium
Potassium Channel
axon terminal
Potency & Duration Differences
Potency
(Less Potent)
Abuse & Reward Pathways
inhibitory
Prior Opiate History Important
opiate-free
taking opiates for pain
never abused opiates
dependent on opiates
currently under the influence of opiates

suggested reading

- **Basic & Clinical Pharmacology, 12th ed. (chapter 31)**
  Bertram G. Katzung, Susan B. Masters, Anthony J. Trevor
- **Pharmacological Basis of Therapeutics, 12th ed. (Chapter 18)**
  Goodman & Gilman

questions:
markbeen@virginia.edu