KETAMINE AND “WIND-UP” PHENOMENON
Objectives

- Quick overview of the neuron and pain pathways
- Go to “Receptorland”
- Discuss traditional pain management techniques
- Discuss the role of Ketamine in attenuating “wind-up”
Wind-Up Phenomenon

- Pain is pain and then its over.
- Wind-Up phenomenon increases pain intensity
- Wind-Up phenomenon increases pain duration
- Wind-Up phenomenon is mediated and attenuated through the NMDA receptor
Wind-Up Phenomenon

- Change in Neural Physiology
- Innocuous Stimuli Becomes Noxious
- Mediated by AMPA, NMDA, and NK₁ Receptors
- Involves the Neurotransmitters Glutamate and Substance P (SP)
- Brain Perceives Pain Even in the Absence of Painful Stimuli
- Occurs Within One Hour
The Neuron

The Synapse

- Nerve impulse
- Axon
- Synapse
- Vesicle
- Neurotransmitters
- Receptor molecules
- Dendrites of receiving neuron
- Direction of impulse
- Axon terminals
- Myelin sheath
- Nucleus
- Cell body
- Axon
- Dendrites
First Order / Second Order

- Synapse
- Axon
- First Order Neuron
- Pain
- Dendrite
- Second Order Neuron
- Soma / Cell Body
Dorsal Root Ganglion

- Dorsal Root Ganglion
- Dorsal Horns
- Synapse
- Spinal Cord
- First Order Neuron
- Receptor
- Free Nerve Ending
Anterolateral Spinothalamic Tract
Spinothalamic Tract (Simplified)

1st Synapse

1st Order Neuron

2nd Order Neuron

2nd Synapse

Thalamus

3rd Order Neuron

Cerebral Cortex

Dorsal

Ventral

DRG

Pain
Spatial Summation

- Synaptic cleft
- Axons
- Postsynaptic terminals
- Presynaptic terminals
- Synapse
- Dendrite
Spatial Summation

What was incision?

What time was antibiotic given?

What's my blood loss?

Patients awake!

Now I understand why they call this the “Blood/Brain Barrier.”

How much Neo?
Temporal Summation
High Intensity Temporal Summation

WHAT ARE YOU DOING TO ME!?!? 

I’m going to show him an “Action Potential.”
Lois, Lois, mom, mom, mummy, mummy, muma, muma, ma, ma, mum, mum, mum, my m

WHAT!!

HI!

Persistent Low Intensity

Temporal Summation

Wind-Up Phenomenon
Review Neuron Physiology and the Action Potential

Last Stop Before “Receptorland”
Ionic Movement (Quick Review)

**Intra-Cellular Fluid**
- Increased K^+ 
- Decreased Na^+ 
- Decreased Ca^{2+} 

**Extra-Cellular Fluid**
- Decreased K^+ 
- Increased Na^+ 
- Increased Ca^{2+} 

All In The Search For Equilibrium
The Action Potential (Quick Review)
Action Potential

Ca^{2+}

Fast Na+ Channels

Increases Na+ Permeability

Impulse / AP Sent

THIS CAN CHANGE
Ah Finally, Receptorland
Speaking The Local Dialect

- Ligands
- Neuroplasticity
  - Up-Regulation
  - Down-Regulation
- Ionotropic Receptors
- Metabotropic Receptors
- Nociceptors / Free Nerve Endings
A Fiber & C Fibers (More Dialect)
Wide Dynamic Range Neuron
alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)
Neurokinin 1 Receptor (NK1r)
N-methyl-D-aspartate (NMDA) Receptor

2nd Order Neuron

Extracellular

Intracellular

KETAMINE
Mu Opioid Receptor
Put The Pieces Together
This Is Very Graphic Material

We Need to Build a Neuron
Where Are We

You Are Here
Our Neurons

Postsynaptic / Second Order Neuron

Threshold -45 Mv
RMP -65 Mv

The Synapse

Presynaptic / First Order Neuron

Threshold -45 Mv
RMP -65 Mv
Under General Anesthesia
Masked Man With A Knife
Initial Pain Impulses

Threshold -45 Mv

Postsynaptic / Second Order Neuron

RMP -65 Mv

Presynaptic / First Order Neuron

Glutamate

Glutamate

Glutamate

Glutamate

Glutamate

Glutamate

Glutamate

Glutamate

Glutamate

Glutamate
More Pain Impulses

Postsynaptic / Second Order Neuron

MUr  NK1r  AMPAr  NMDAr  MUr  MUr

Glutamate  Glutamate  Glutamate  Glutamate  Glutamate

Threshold -45 Mv  RMP -65 Mv

Presynaptic / First Order Neuron

MUr
Increased Pain Impulses

**Postsynaptic / Second Order Neuron**

- **Threshold** -45 Mv
- **RMP** -65 Mv

**Presynaptic / First Order Neuron**
NMDA Receptor
Beginnings of Wind-Up Phenomenon

**Postsynaptic / Second Order Neuron**

- **Threshold** -45 Mv
- **RMP** -60 Mv

**Presynaptic / First Order Neuron**

- **Glutamate**
- **Na+**

**NMDAr**

**MUr**

**NK1r**

**AMPAr**

**MUr**

**MUr**

**MUr**
Wind-Up Phenomenon

Threshold -45 Mv
RMP -60 Mv

Phospholipase-C → DAG → PKC

Na+ Na+ Na+ Na+ Na+

Glutamate Glutamate Glutamate Glutamate Glutamate

Na+ Ca++

Presynaptic / First Order Neuron
Wind-Up Phenomenon

- **Threshold**: -45 Mv
- **RMP**: -50 Mv

**Presynaptic / First Order Neuron**

- **MUr**
- **NK1r**
- **AMPAr**
- **NMDAr**

- **CaMKII**
- **Na+**
- **Ca++**

- **Glutamate**
- **SP**

- **MUr**

- **Threshold**: -45 Mv
- **RMP**: -50 Mv
Hyperalgesia / Allodynia

Threshold -45 Mv
RMP -50 Mv

Pain

Na+ Na+ Na+ Ca++

Glutamate Glutamate Glutamate Glutamate

Na+ Na+

Glutamate Glutamate

Na+

Glutamate

Na+

Glutamate

Na+

Glutamate Glutamate

Pain

Pain

Pain

Pain

MUr

NK1r

AMPAr

NMDAr

MUr

MUr

MUr

Presynaptic / First Order Neuron
Wind-Up on the WDR Neuron
Traditional Opioids

Threshold -45 Mv
RMP -65 Mv

Presynaptic / First Order Neuron
RMP -65 Mv
Opioid Problem

Presynaptic / First Order Neuron

Threshold -45 Mv
RMP -65 Mv
RMP -55 Mv
RMP -50 Mv

Pain

Pain

Pain

NK1r

MUr

NK1r

AMPAr

NMDAr

MUr

MUr

K+

K+

K+

Na+

Na+

Na+

Na+

Na+

Na+

Glutamate

Glutamate

Glutamate

Glutamate

Glutamate

Glutamate

SP

SP

SP

SP

SP

SP

SP

SP

SP

SP

SP

SP

SP

SP

SP

SP

SP

Pain

Pain

Pain

Fentanyl

Fentanyl

Fentanyl

Fentanyl

Fentanyl

Fentanyl

K+

K+

K+
Opioid Problem

Threshold: -45 mV
RMP: -65 mV

Presynaptic / First Order Neuron

Pain

I'm out of gas!
Help!
Let's see if we can put some "Tomcats" in the air.
Ketamine

Threshold -45 Mv
RMP -65 Mv

RMP -50 Mv RMP -65 Mv

Presynaptic / First Order Neuron

RMP -65 Mv
Practicality of Ketamine
How Much Ketamine?

- Less Painful Procedures
  - 0.25mg / Kg Prior to Incision
  - 0.125mg / Kg every 30 minutes
  - Infusion 0.25mg/kg/hr
  - Last dose 30 min prior to emergence

- Painful Procedures
  - 0.5mg / Kg prior to Incision
  - 0.25mg / Kg every 30 minutes
  - Infusion 0.5mg/kg/hr
  - Last dose 60 min prior to emergence
Myths of Sub-Anesthetic Ketamine

- Ketamine and emergence phenomenon
- Ketamine and PONV
- Ketamine and ischemic heart disease

Using high dose narcotics → do not need ketamine
The Anesthetists Toolbox