Beyond Traditional Assessments of Pain: What can animals tell us about analgesic efficacy?

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11th Annual Pain Consortium Symposium
May 31, 2016
Bethesda, Maryland
A Historical Introduction

Ancient Cultures
Pain: A Historical Introduction

Adapted from Guindon and Hohmann HNBS, 2009
Pain: A Historical Introduction

Descartes 1664

Max von Frey² 1894-1895

Specificity theory

Ancient Cultures

1842 Müller

Doctrine of specific nerve energies

1927 Pavlov

Appetites

Pain

Emotions

Pleasure

Opposite

US (food)

UR (salivation)

CS (electric, burn, cut)

CR (salivation)

US (food) paired with CS (shock, burn, cut)

Adapted from Guindon and Hohmann HNBS, 2009
Pain: A Historical Introduction

Specificity theory
- Ancient Cultures
- 1842 Müller

Pattern theory
- 1894-1895 Max von Frey
- 1894 Goldscheider
- 1943 Livingston

Specificity theory
- Pain
- appetites
- emotions

Pattern theory
- US (food)
- UR (salivation)
- US (food) paired with CS (shock, burn, cut)
- CR (salivation)

Gate-control system
- Input
- Action system
- central control

Adapted from Guindon and Hohmann HNBS, 2009
Pain: A Historical Introduction

Descartes 1664

Specificity theory

Pattern theory

Ancient Cultures

1842 Müller

1927 Pavlov

1965 Melzack & Wall

Pleasure

opposite

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Doctrine of specific nerve energies

US (food) paired with CS (shock, burn, cut)

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Pain: A Historical Introduction

Specificity theory

- Ancient Cultures
  - appetites
  - Pain
  - emotions
  - opposite
  - Pleasure

Pattern theory

- 1842 Müller
- 1927 Pavlov
- 1965 Melzack & Wall

- Descartes 1664
- Max von Frey 1894
- Goldscheider 1894
- Livingston 1943
- Akil & Liebeskind 1976
- Animal model of neuropathic pain
  - Bennett & Xie 1988

Specificity theory:
- Doctrine of specific nerve energies

Pattern theory:
- US (food)
- UR (salivation)
- US (food) paired with CS (shock, burn, cut)

Adapted from Guindon and Hohmann HNBS, 2009
The Drug Development Process is Lengthy

- Discovery and early in vitro screening of compound
- Large-scale synthesis
- Animal testing

Preclinical research:
- Investigational new drug application sent to FDA
- New drug application sent to FDA
- Approval

Clinical studies:
- Phase 1: 1.5 years
- Phase 2: 2 years
- Phase 3: 3.5 years

Postmarketing surveillance:
- Monitor adverse reactions, product defects, long term side effects, drug interactions

Duration:
- Preclinical research: At least 5 years
- Clinical studies: 7 years
- Review by FDA: 1.5 years
- Ongoing
The Drug Development Process is Lengthy

12-14 years

Stephanie Florio, Anagin LLC
Small Molecules: High Attrition Rate

The vast majority of compounds will never make it into the clinic…

Stephanie Florio, Anagin LLC
Working Hypothesis

- Animals will self-medicate with a ‘nonpsychoactive’ cannabinoid analgesic to attenuate a neuropathic pain state
**CB₁ receptors**

- Abundant in central nervous system (CNS)

**CB₂ receptors**

- Primarily in the immune tissues and cells
- Low level in the CNS

Sobotta: Atlas der Anatomie des Menschen © Elsevier
Central Nervous System Side-effects

- Antinociception
- Hypothermia
- Hypoactivity
- Motor Ataxia
Cannabinoid CB$_2$ Mechanisms

• Suppresses neuropathic pain without CNS side-effects associated with activation of CB$_1$
  
• Hypoactivity
• Hypothermia
• Tail-flick Antinociception
• Catalepsy
• Tolerance
• Physical dependence
Cannabinoid CB$_2$ Mechanisms

- Suppresses development and maintenance of neuropathic pain
- Absent in CB2 KO and preserved in CB1 KO mice
- Suppresses proinflammatory cytokine and chemokine expression
- Suppress windup and Fos protein expression in spinal dorsal horn neurons
- Separation of Analgesic Efficacy and Drug Abuse Liability?
Spared Nerve Injury (SNI)

Decosterd and Woolf (2000) Pain 87: 149-158
Drug Self-administration Apparatus
Assessment of Mechanical Paw Withdrawal Thresholds
Spared Nerve Injury Decreases Mechanical Paw Withdrawal Thresholds

Gutierrez et al. Pain 2011
Self-administration of AM1241 Induces CB$_2$-mediated Anti-allodynic Effects in the Left (Injured) Paw

Gutierrez et al. Pain 2011
The CB₂ Antagonist SR144528 Blocks AM1241 Self-administration in Neuropathic Rats

Gutierrez et al. Pain 2011
Neuropathic Rats Work Harder than Shams to Obtain AM1241 When the Schedule of Reinforcement is Increased

Gutierrez et al. Pain 2011
AM1241 Self-Medication Suppresses Neuropathic Nociception on Different FR Schedules

Gutierrez et al. Pain 2011
Active Lever Responding for AM1241 is Similar to Vehicle in Naïve Animals

Gutierrez et al. Pain 2011
Self-administration of AM1241, but not Vehicle, Increases Mechanical Withdrawal Thresholds in the Left (Injured) Paw in Neuropathic Rats

Gutierrez et al. Pain 2011
Extinction Decreases Lever Pressing for AM1241

![Graph showing the decrease in lever pressing for AM1241 compared to Vehicle.](Gutierrez et al. Pain 2011)
SUMMARY: Self-Medication

- Neuropathic animals self-medicated with a CB$_2$ agonist to attenuate neuropathic pain behavior
- Neuropathic animals worked harder than shams to obtain the CB$_2$ agonist
- Naïve animals did not reliably self-administer the CB$_2$ agonist
- Naïve, sham and neuropathic rats self-administered morphine
- In an extinction test, neuropathic animals perseverated in responding on the lever previously paired with the opioid analgesic but not with the CB$_2$ agonist
CONCLUSIONS

• CB₂ agonists can suppress neuropathic pain in preclinical models without producing tolerance, CB₁-dependent withdrawal, reward or cardinal signs of CB₁ receptor activation

• Neuropathic rats self-administer a CB₂ agonist for its negative reinforcing properties (i.e. ability to attenuate a neuropathic pain state)

• Opioid analgesics exhibit higher abuse liability in neuropathic pain states compared to CB₂ agonists

• Operant methods represent promising experimental approaches for elucidating both analgesic efficacy and drug abuse liability
A History Of Medicine

• 2000 B.C. - Here, eat this root.
• 1000 A.D. - That root is heathen. Here, say this prayer.
• 1850 A.D. - That prayer is superstition. Here, drink this potion.
• 1940 A.D. - That potion is snake oil. Here, swallow this pill.
• 1985 A.D. - That pill is ineffective. Here, take this antibiotic.
• 2016 A.D. - That antibiotic is artificial. Here, eat this root.
ACKNOWLEDGMENTS

NIDA
• DA14022, DA14265, DA021644, DA028200

Indiana University
• Tannia Gutierrez
• Liting Deng
• Jon Crystal

University of Georgia
• Elizabeth Rahn
• Andrea Nackley

Northeastern University
• Alexandros Makriyannis
• Alexander Zvonok