

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

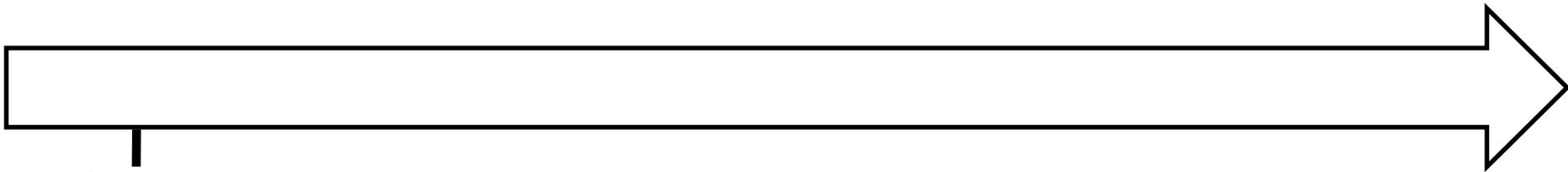
Andrea G. Hohmann

Indiana University

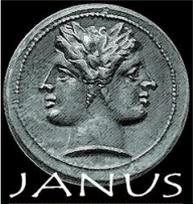
11th Annual Pain Consortium Symposium
May 31, 2016
Bethesda, Maryland



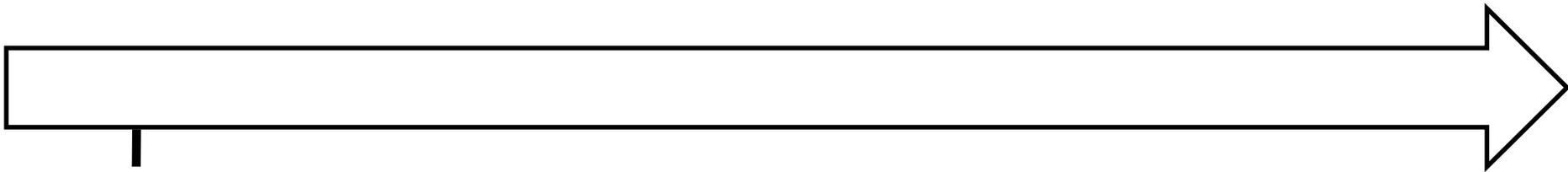
A Historical Introduction



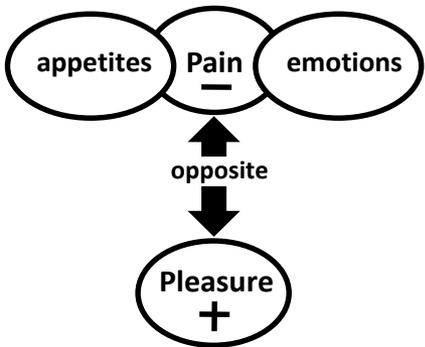
Ancient Cultures



Pain: A Historical Introduction



Ancient Cultures



Pain: A Historical Introduction



Descartes
1664

Max von Frey²
1894-1895

Specificity theory

Ancient Cultures

appetites Pain emotions

opposite

Pleasure

1842
Müller

Doctrine of
specific nerve
energies



1927
Pavlov

US (food)

UR (salivation)

CS (electric,
burn, cut)

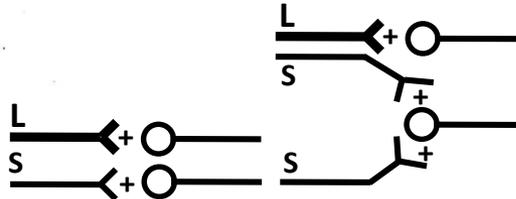
CR (salivation)

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

Pain: A Historical Introduction



Descartes
1664



Theory of
cutaneous
senses

Summation
theory

Max von Frey²
1894-1895

Goldscheider
1894

Model of
reverberatory
circuits
Livingston
1943

Specificity theory

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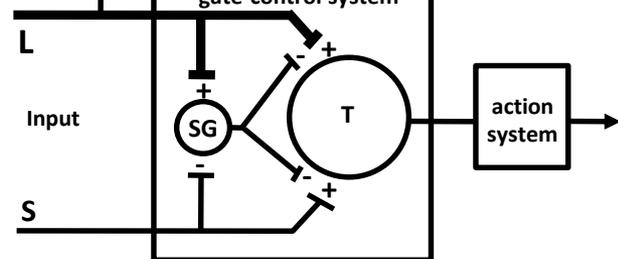


US (food)
↓
UR (salivation)

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

CS (electric,
burn, cut)
↓
CR (salivation)

central
control
gate-control system

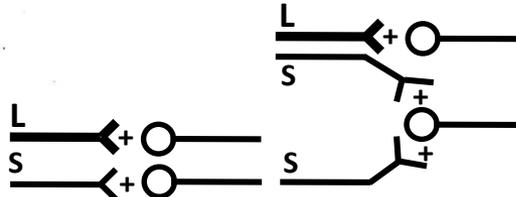


Adapted from Guindon and Hohmann HNBS, 2009

Pain: A Historical Introduction



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1664



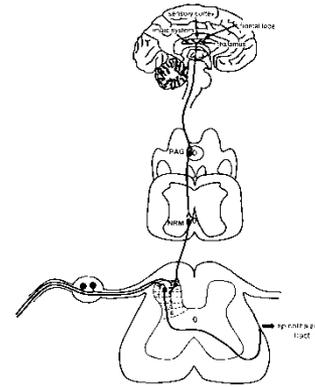
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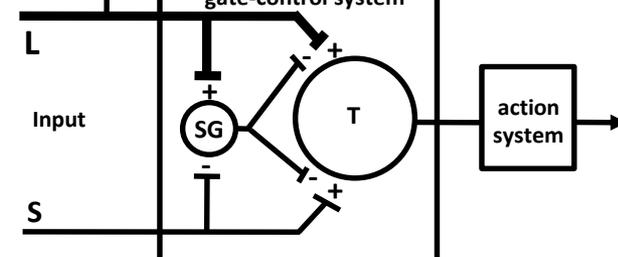
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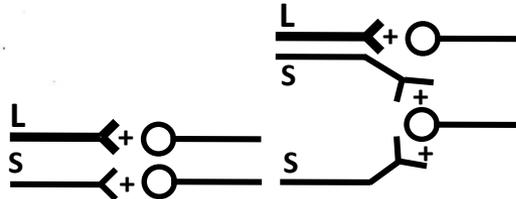


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Pain: A Historical Introduction



Descartes
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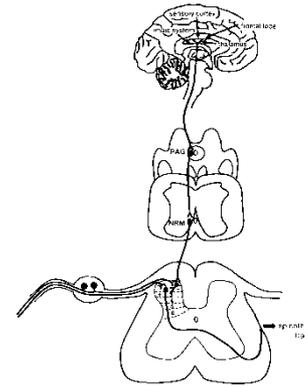
Theory of cutaneous senses

Max von Frey²
1894-1895

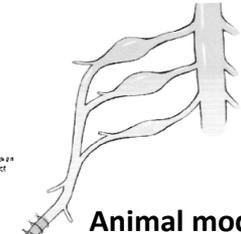
Summation theory

Goldscheider
1894

Model of reverberatory circuits
Livingston
1943



Akil & Liebeskind
1976



Animal model of neuropathic pain
Bennett & Xie
1988

Specificity theory

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Ancient Cultures

1842
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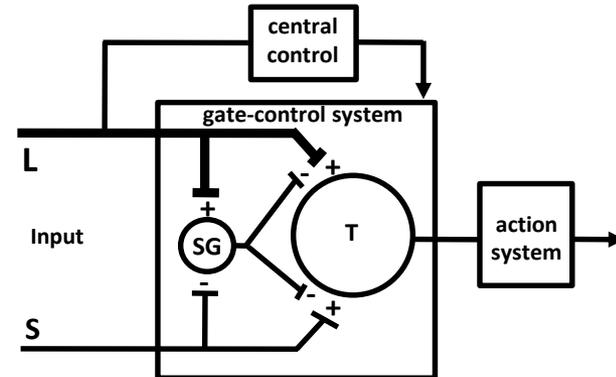
Doctrine of specific nerve energies



US (food)
UR (salivation)

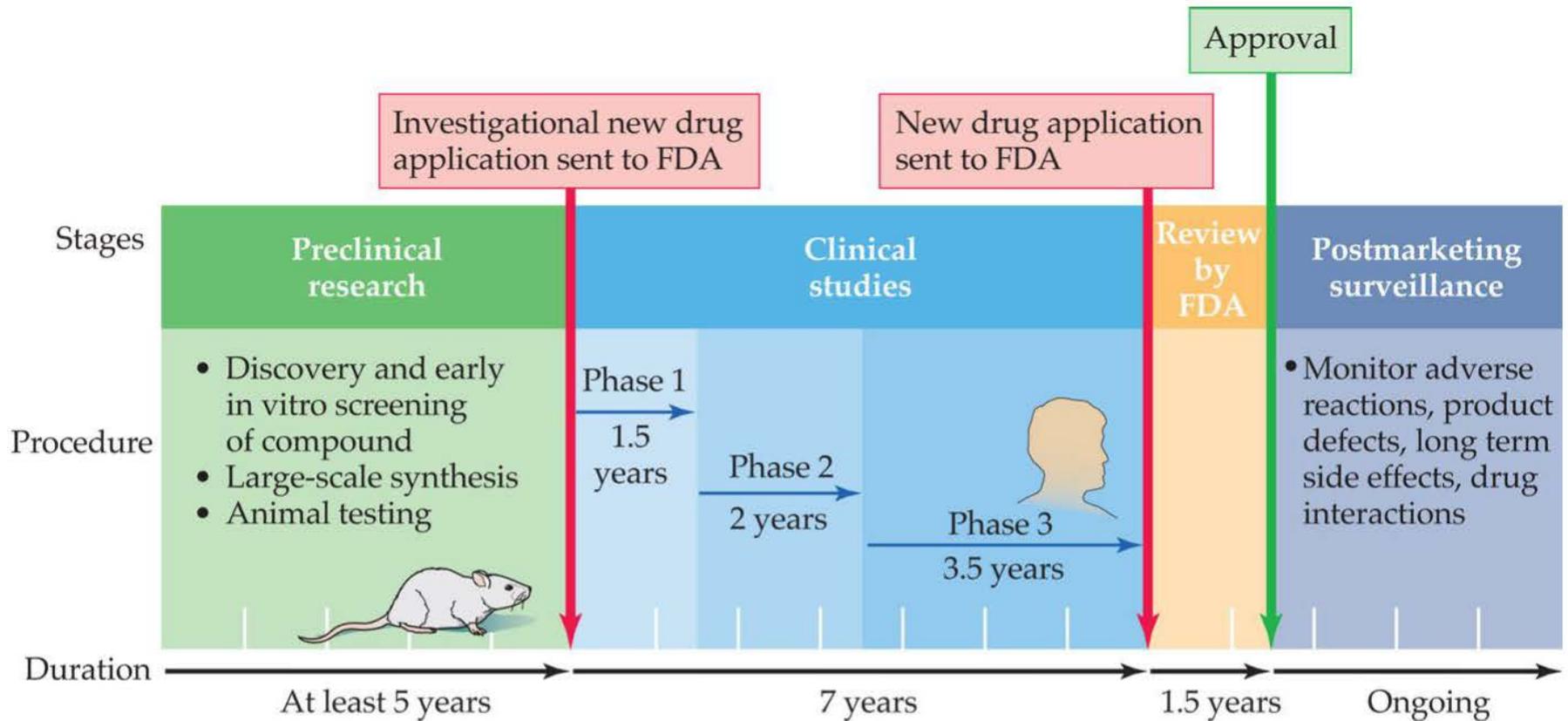
US (food) paired with CS (shock, burn, cut)

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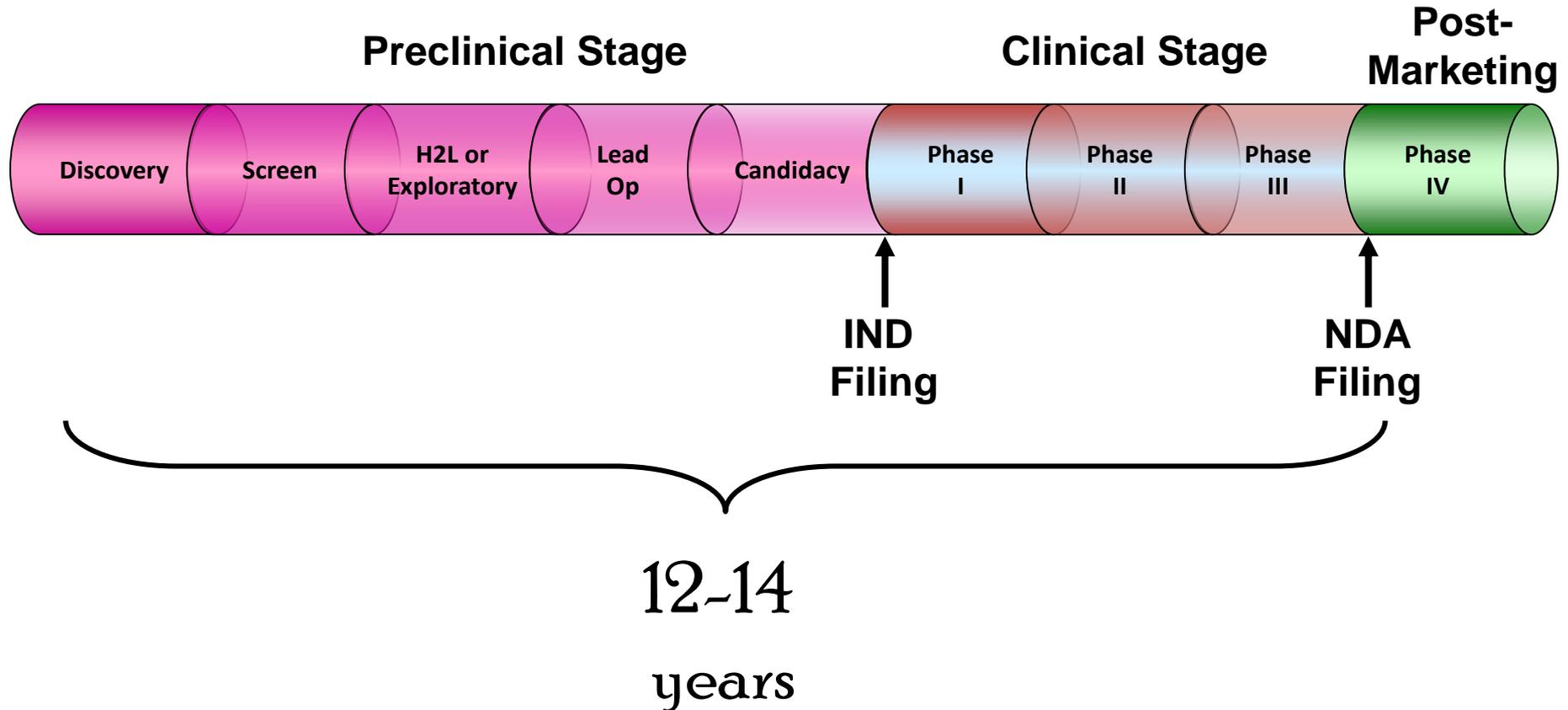
The Drug Development Process is Lengthy



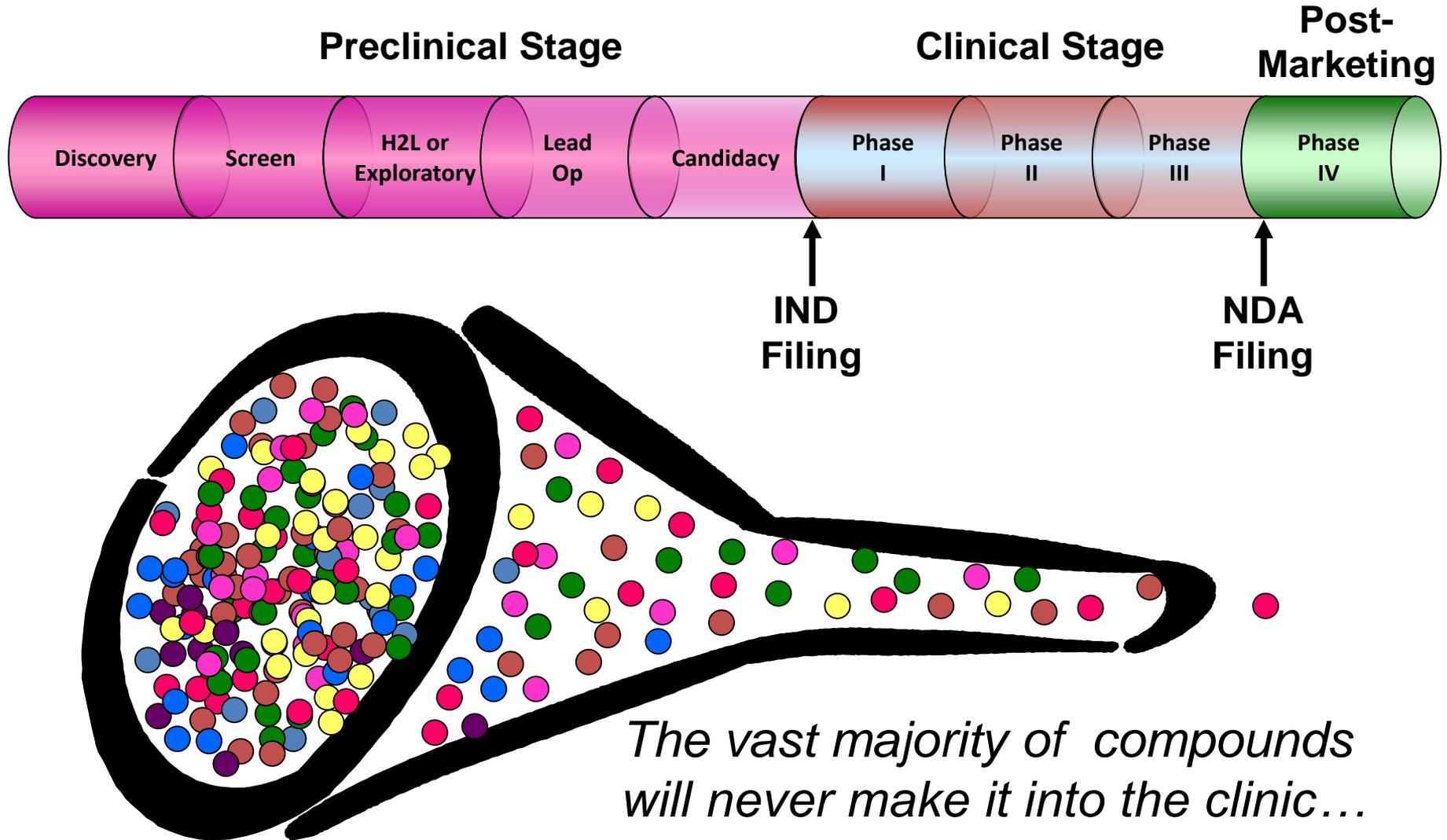
PSYCHOPHARMACOLOGY 2e, Box 4.2, Figure A

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The Drug Development Process is Lengthy

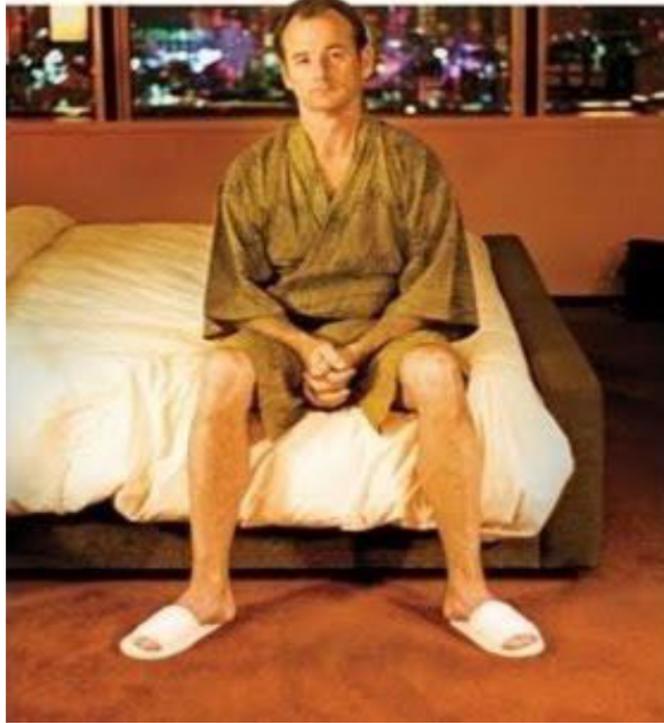


Small Molecules: High Attrition Rate



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

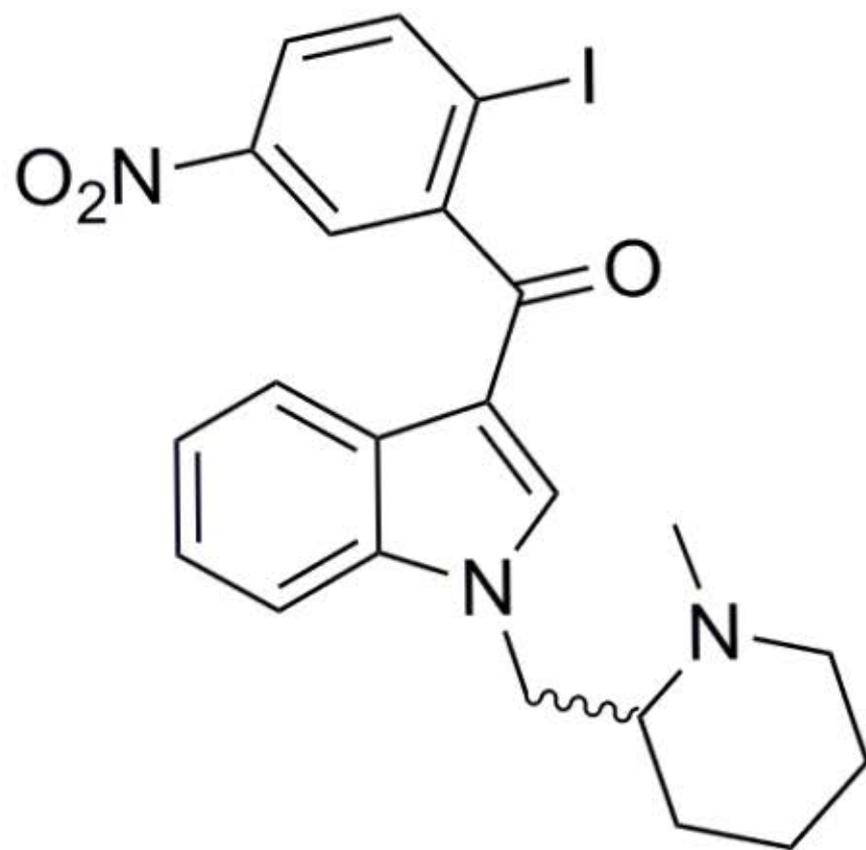
LOST IN TRANSLATION



?

Working Hypothesis

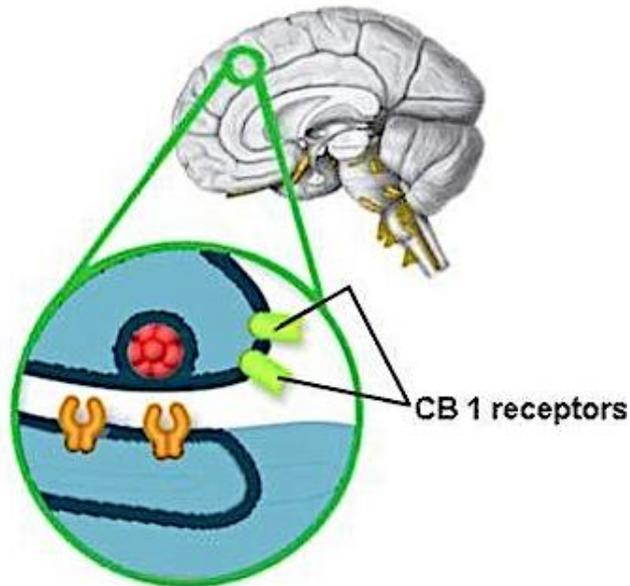
- Animals will self-medicate with a 'nonpsychoactive' cannabinoid analgesic to attenuate a neuropathic pain state



(R,S)-AM1241

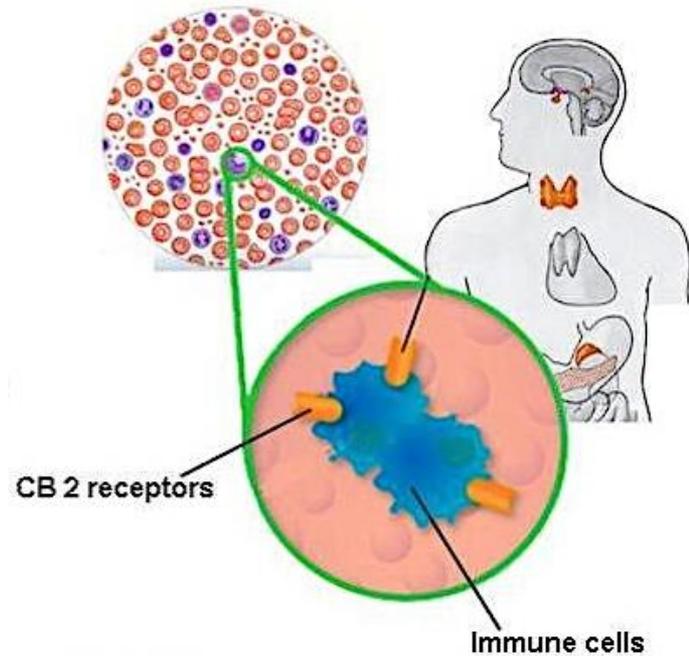
CB₁ receptors

- Abundant in central nervous system (CNS)



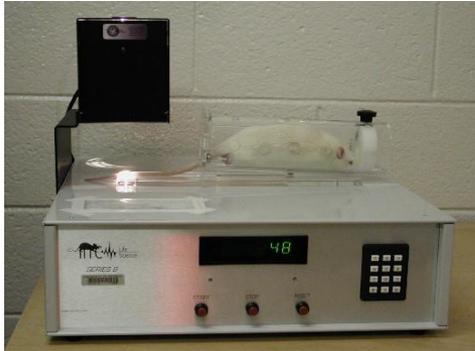
CB₂ receptors

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



Central Nervous System Side-effects

Antinociception



Hypothermia



Hypoactivity



Motor Ataxia

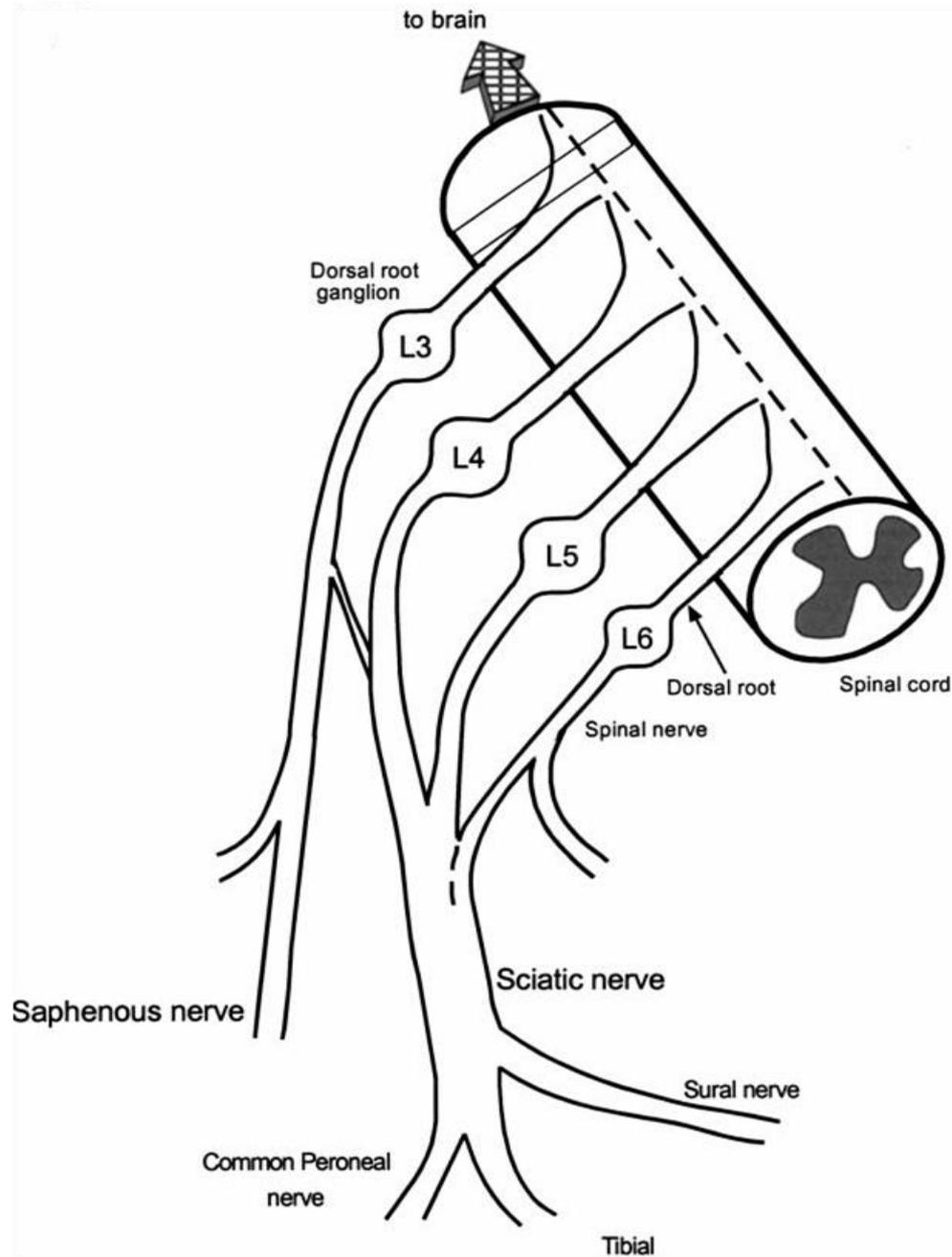


Cannabinoid CB₂ Mechanisms

- Suppresses neuropathic pain without CNS side-effects associated with activation of CB₁
 - Hypoactivity
 - Hypothermia
 - Tail-flick Antinociception
 - Catalepsy
 - Tolerance
 - Physical dependence

Cannabinoid CB₂ 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?



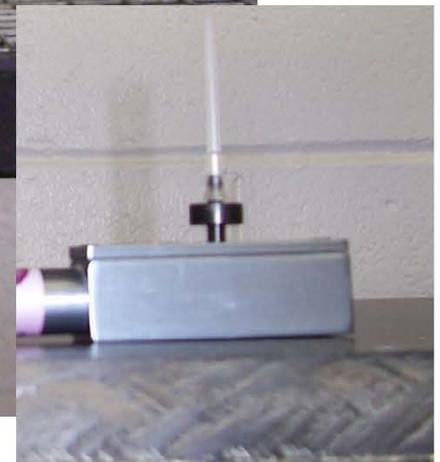
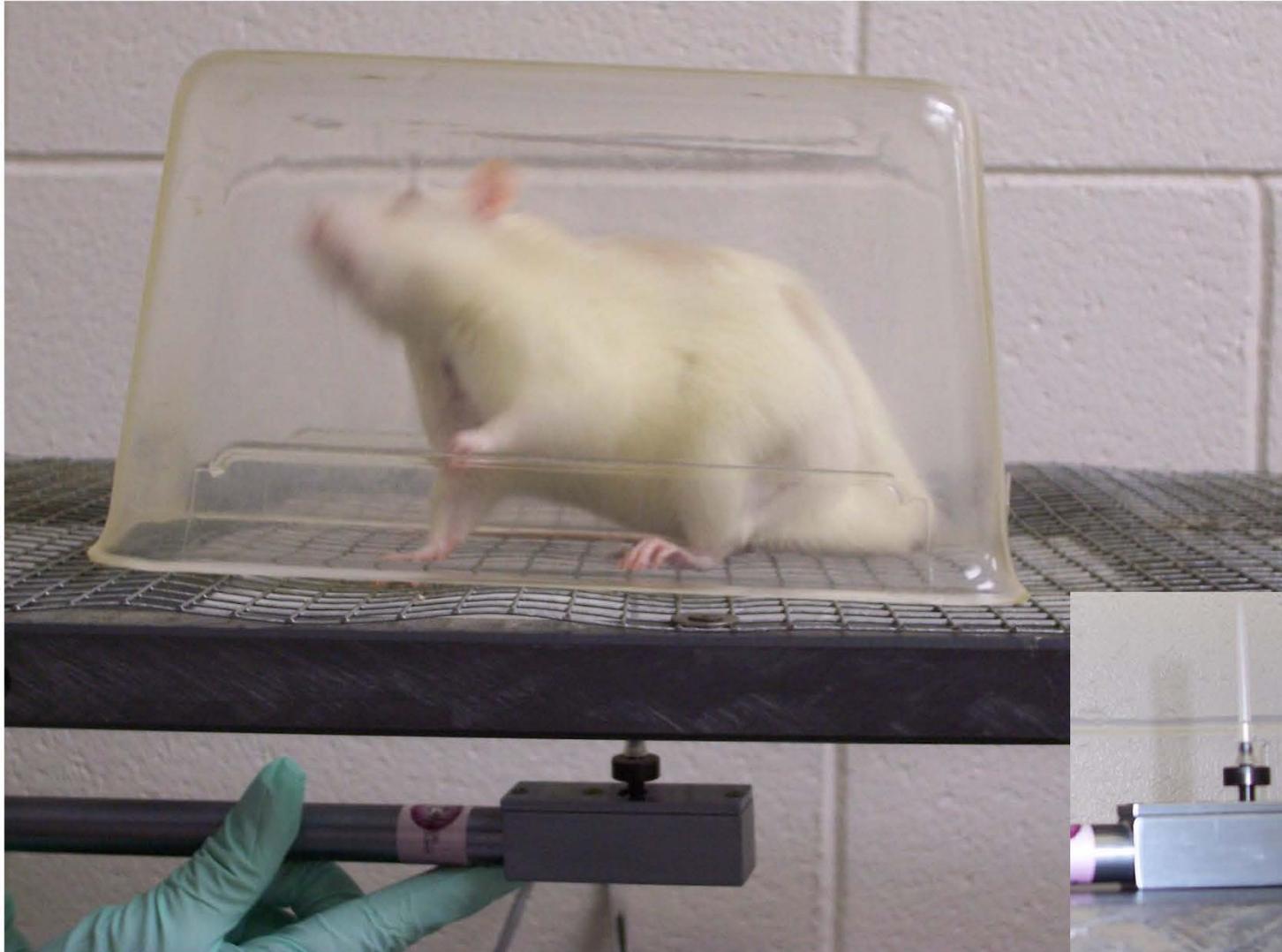
Spared Nerve Injury (SNI)

Decosterd and Woolf
(2000) Pain 87: 149-158

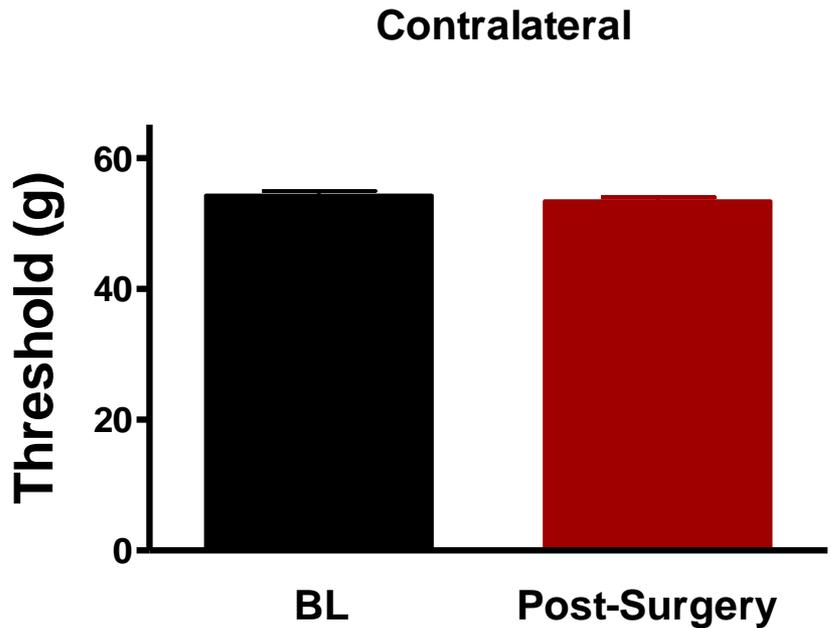
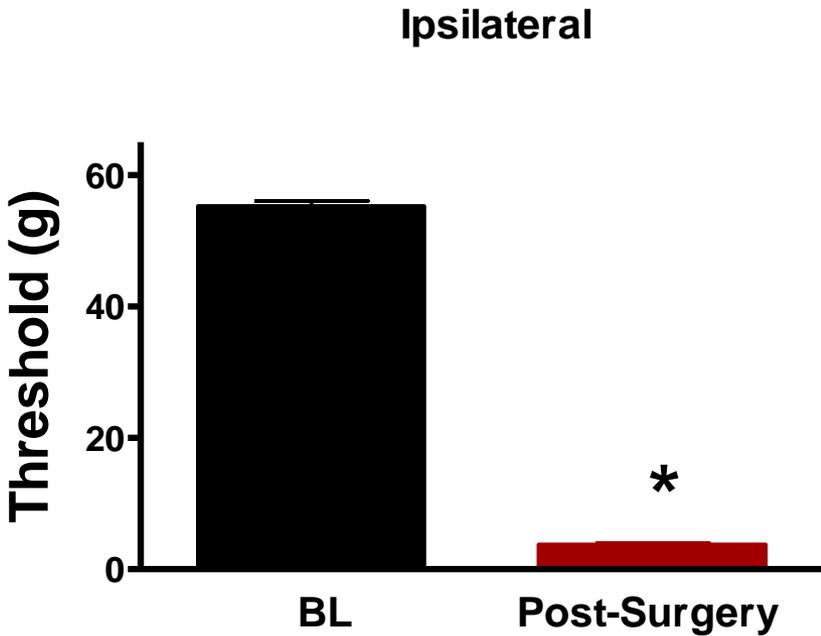
Drug Self-administration Apparatus



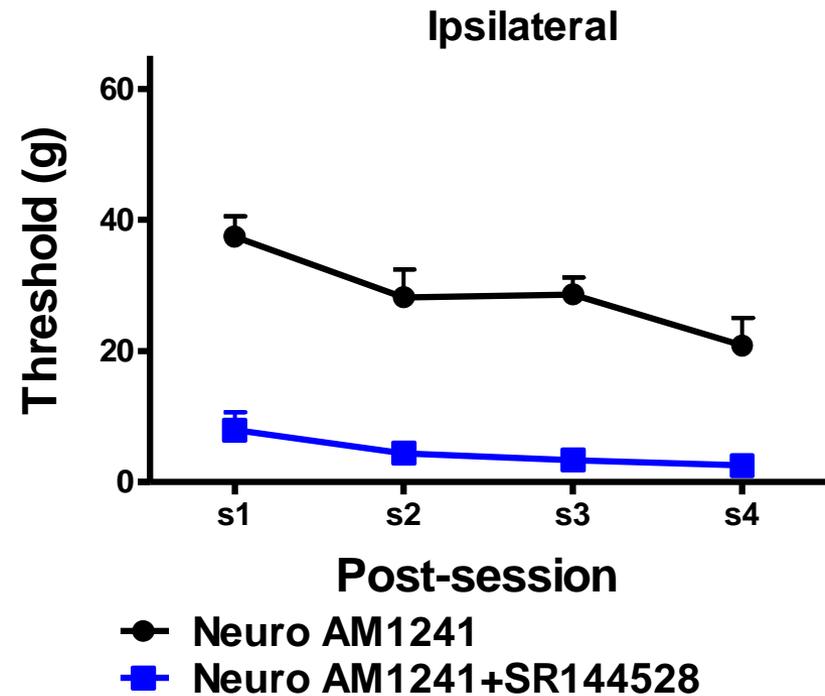
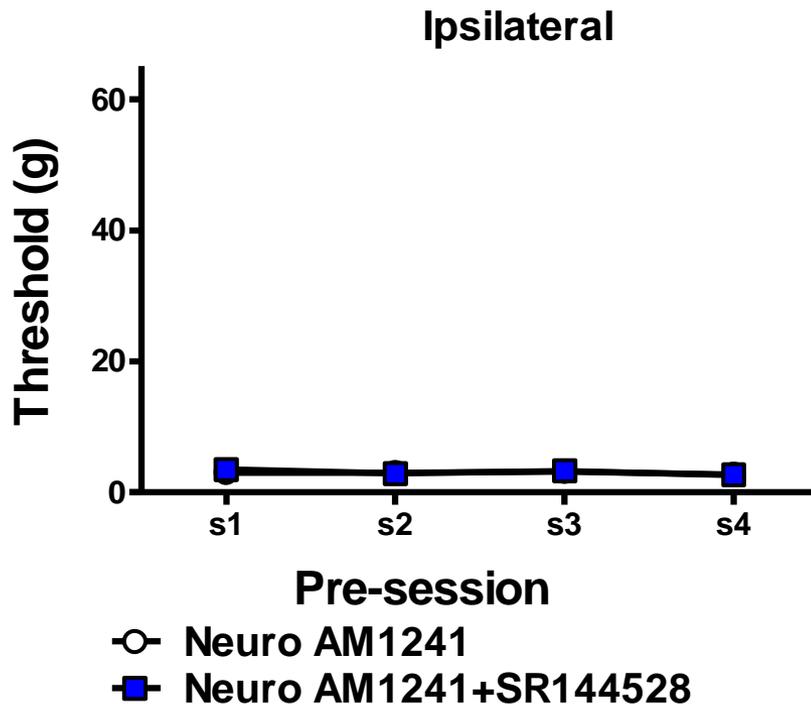
Assessment of Mechanical Paw Withdrawal Thresholds



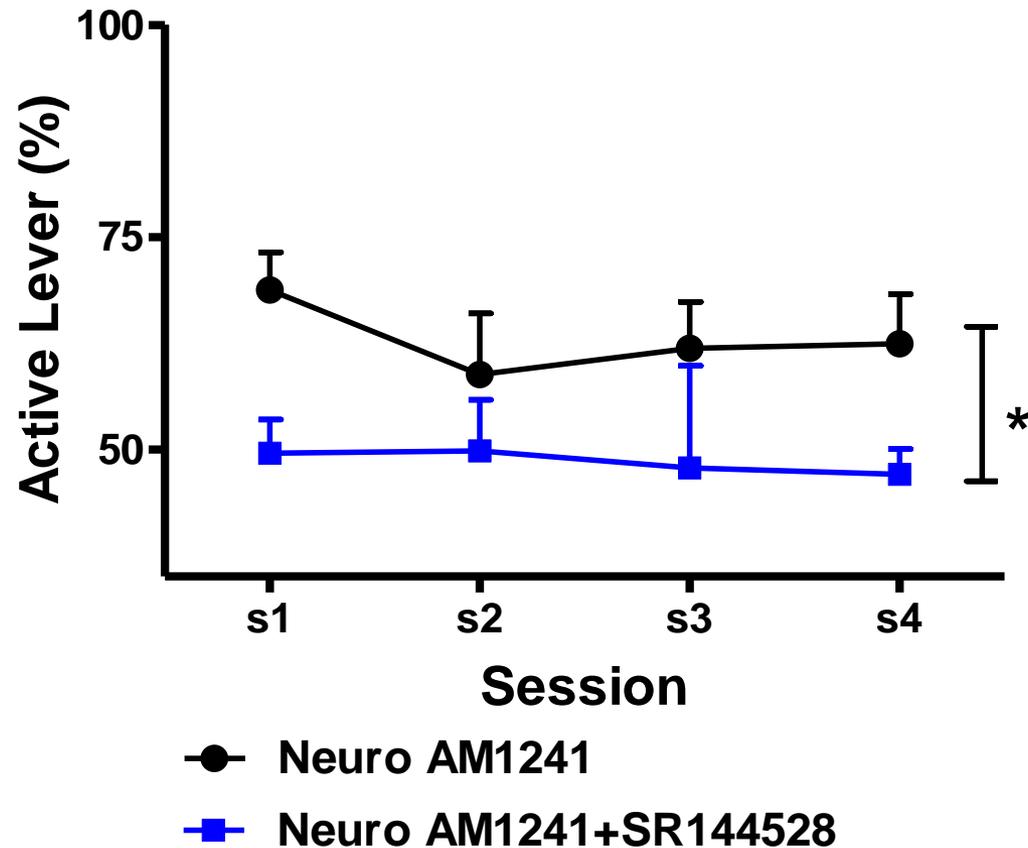
Spared Nerve Injury Decreases Mechanical Paw Withdrawal Thresholds



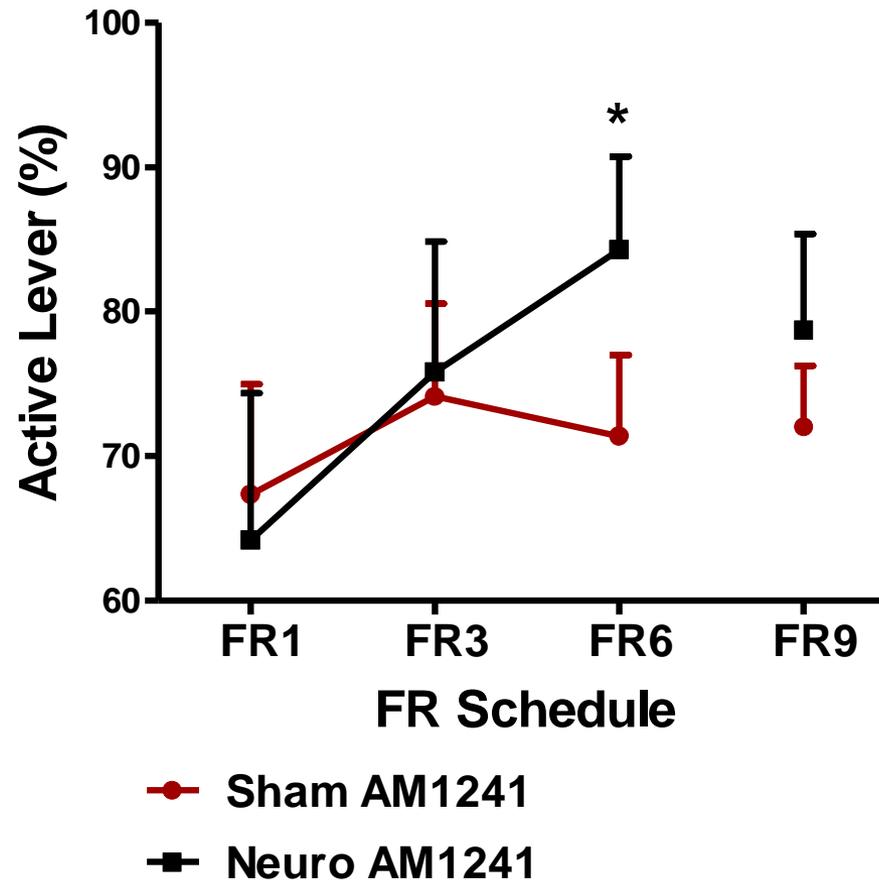
Self-administration of AM1241 Induces CB₂-mediated Anti-allodynic Effects in the Left (Injured) Paw



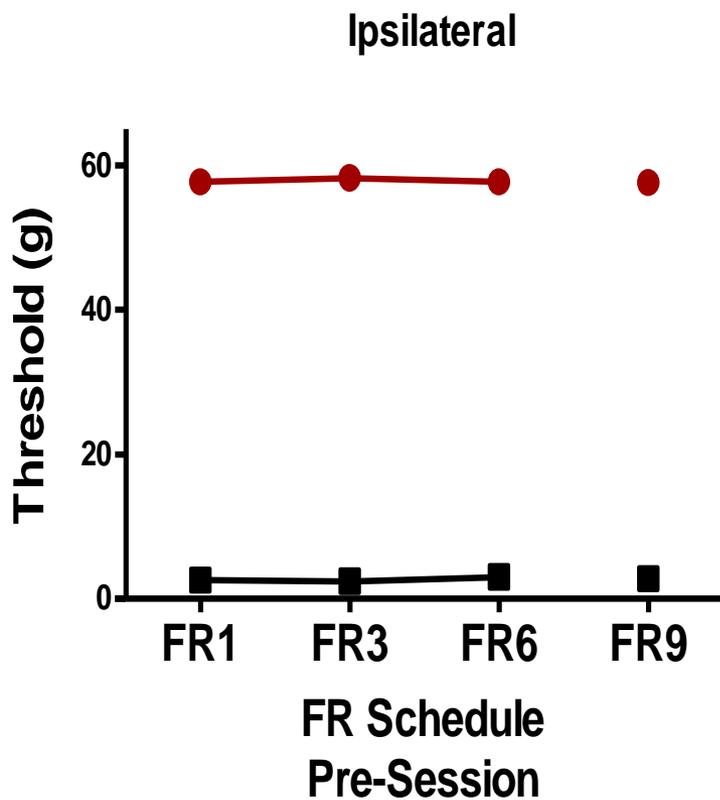
The CB₂ Antagonist SR144528 Blocks AM1241 Self-administration in Neuropathic Rats



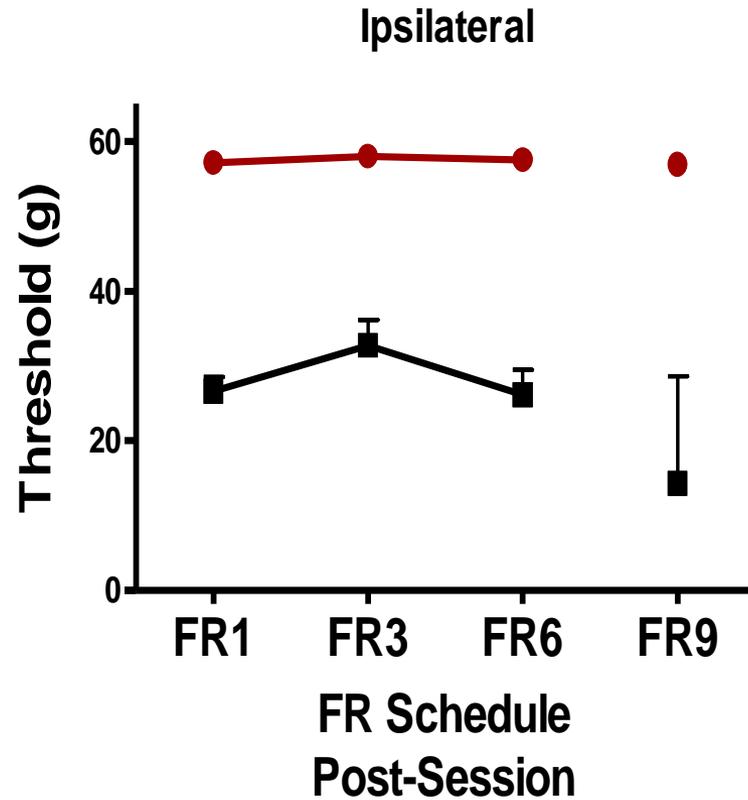
Neuropathic Rats Work Harder than Shams to Obtain AM1241 When the Schedule of Reinforcement is Increased



AM1241 Self-Medication Suppresses Neuropathic Nociception on Different FR Schedules

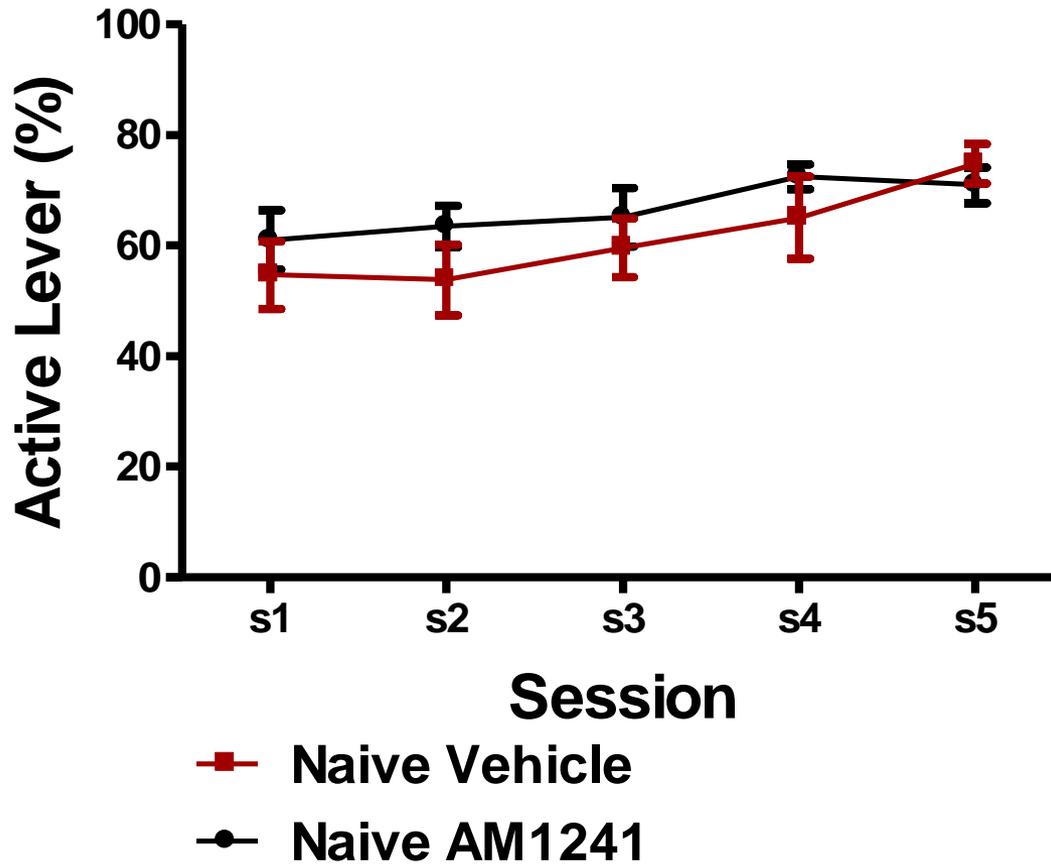


- Sham AM1241
- Neuro AM1241

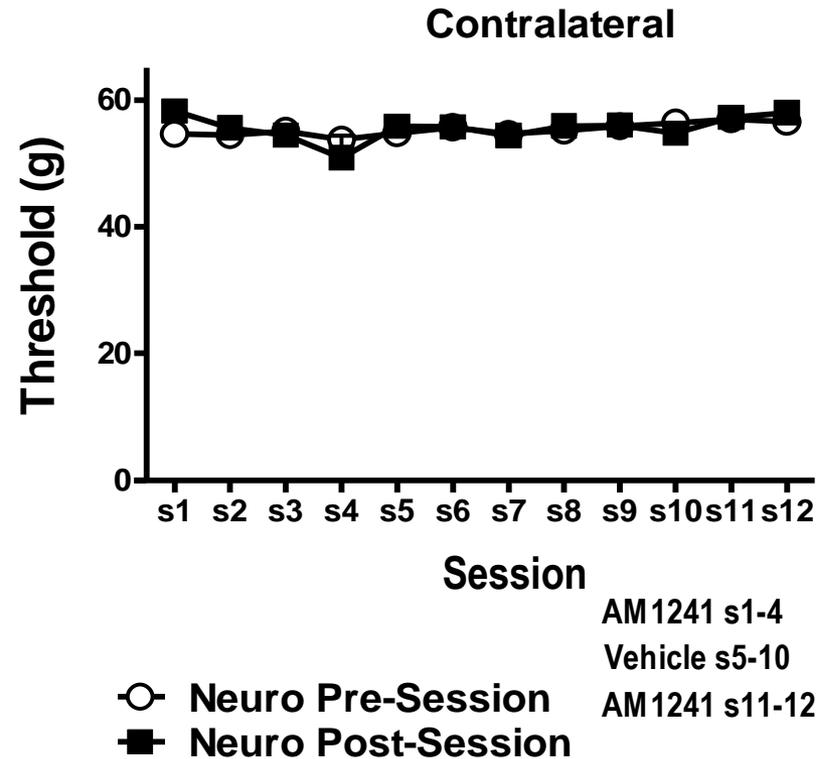
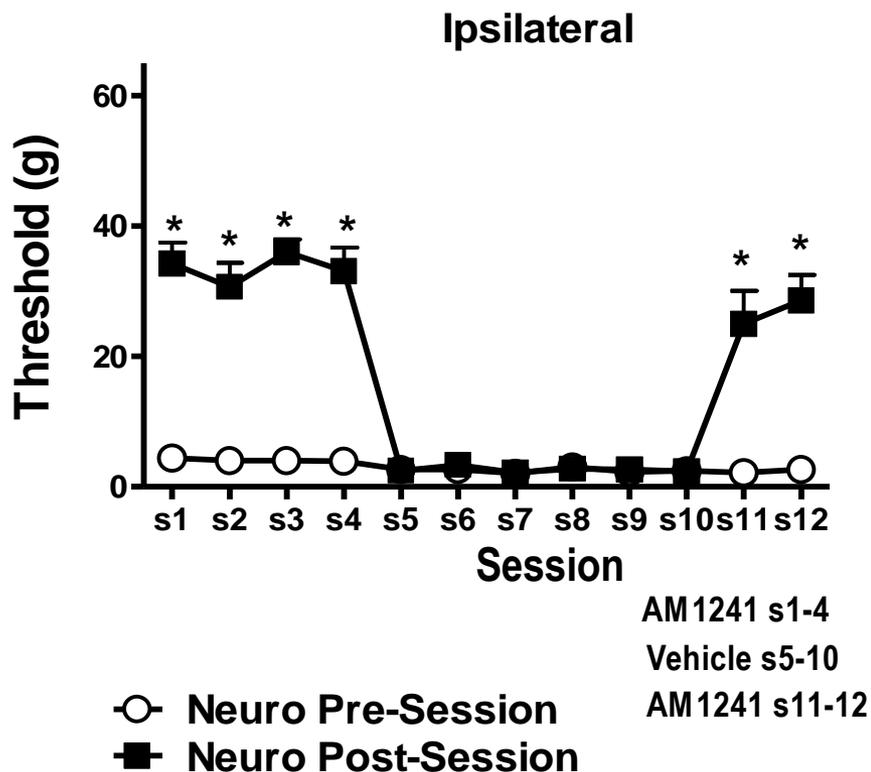


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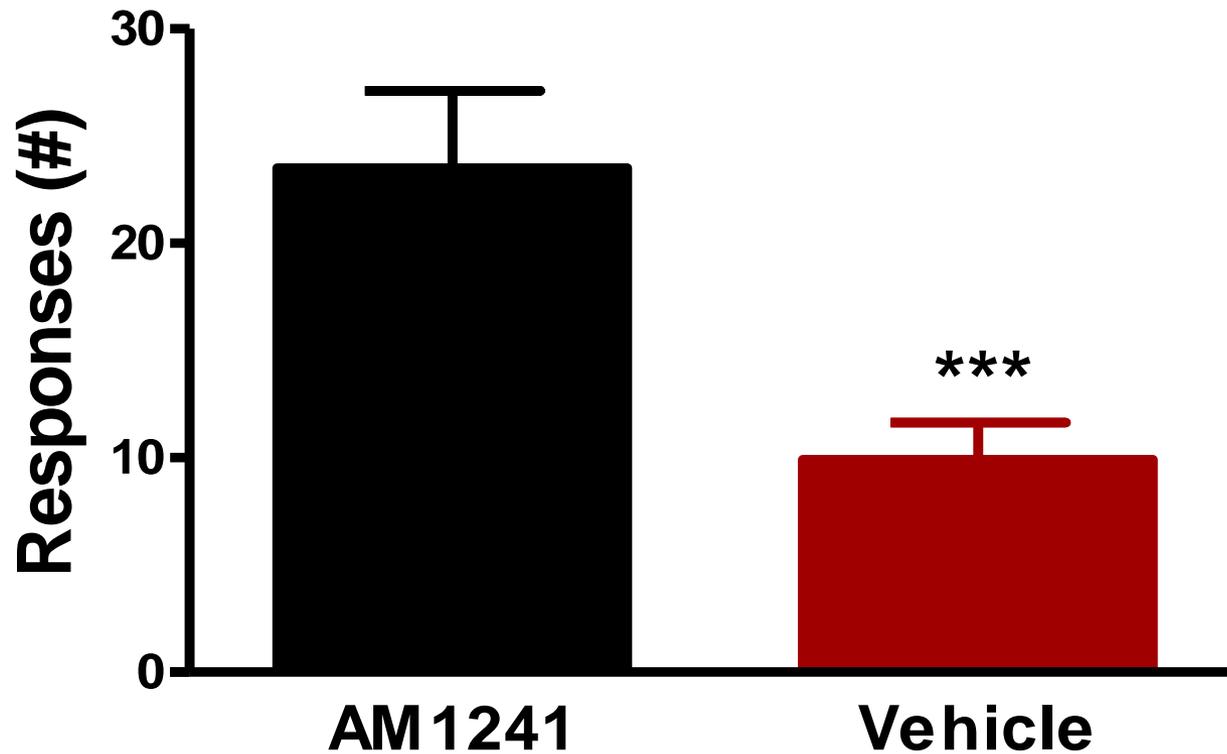
Active Lever Responding for AM1241 is Similar to Vehicle in Naïve Animals



Self-administration of AM1241, but not Vehicle, Increases Mechanical Withdrawal Thresholds in the Left (Injured) Paw in Neuropathic Rats



Extinction Decreases Lever Pressing for AM1241

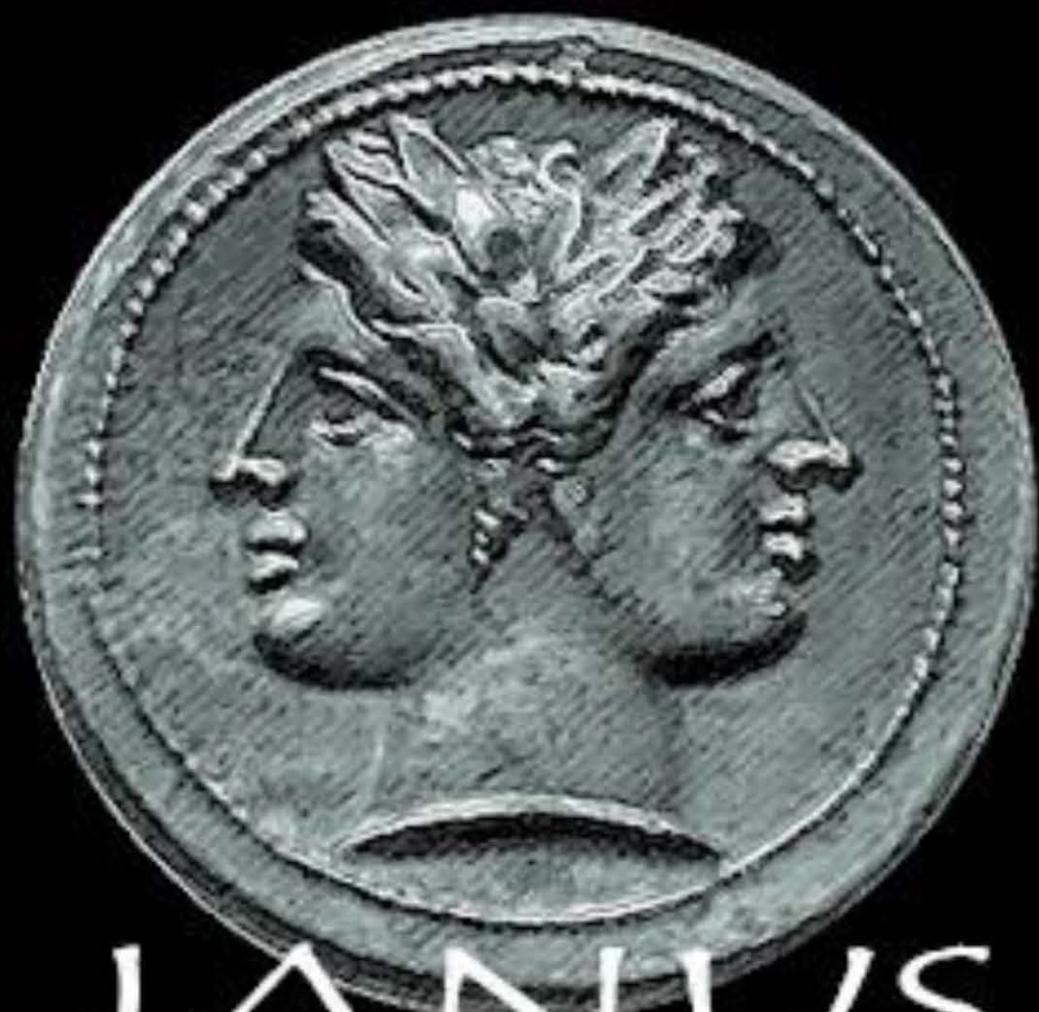


SUMMARY: Self-Medication

- Neuropathic animals self-medicated with a CB₂ agonist to attenuate neuropathic pain behavior
- Neuropathic animals worked harder than shams to obtain the CB₂ agonist
- Naïve animals did not reliably self-administer the CB₂ 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 CB₂ 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



JANUS

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

Northeastern University

- Alexandros Makriyannis
- Alexander Zvonok

University of Georgia

- Elizabeth Rahn
- Andrea Nackley