A Dual Fatty Acid Amide Hydrolase and Monoacylglyercol Lipase Inhibitor Produces Opioid Sparing Analgesic Effects in Mice

Jenny L. Wilkerson, Ph.D.

Virginia Commonwealth University

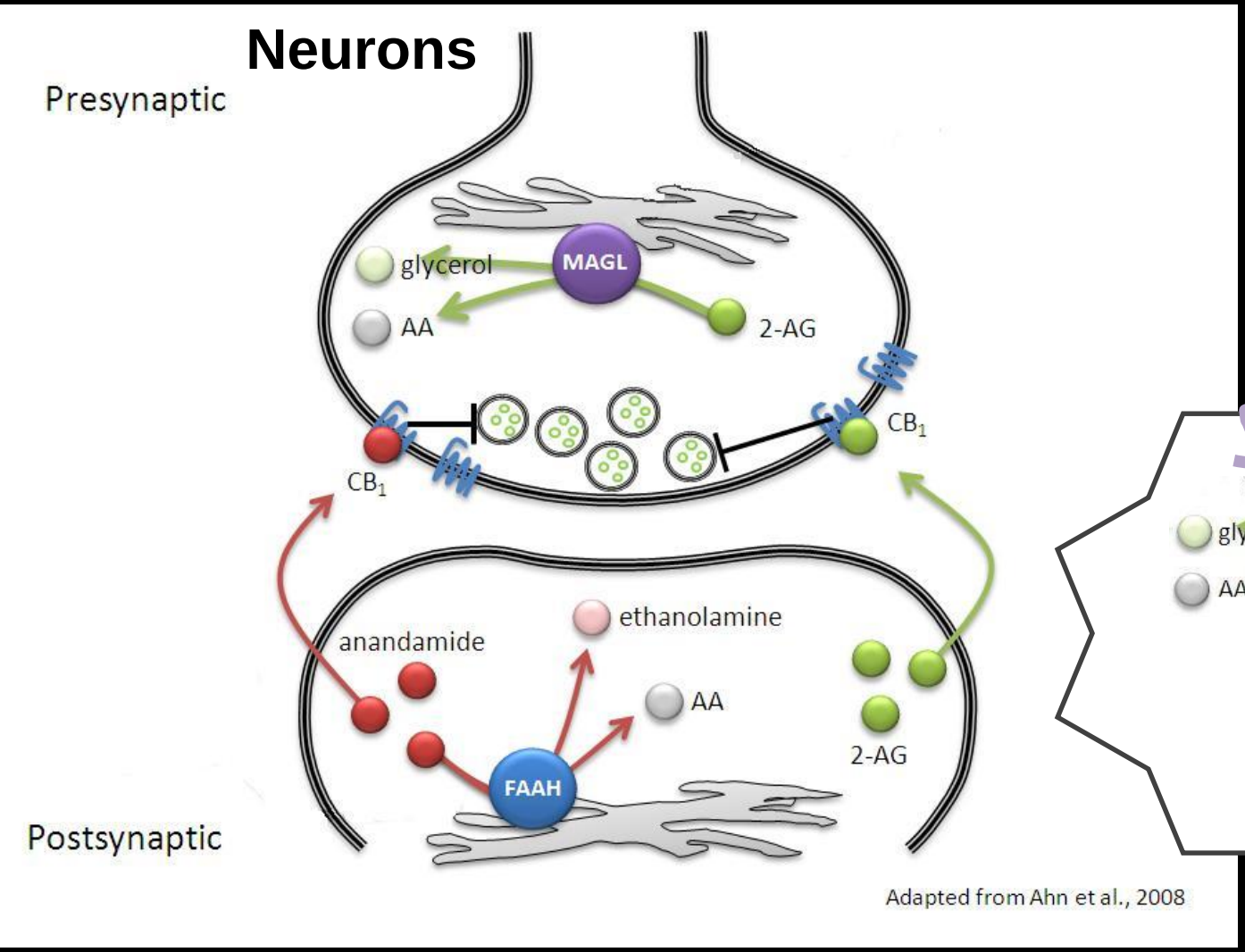
Department of Pharmacology & Toxicology

Lichtman Lab

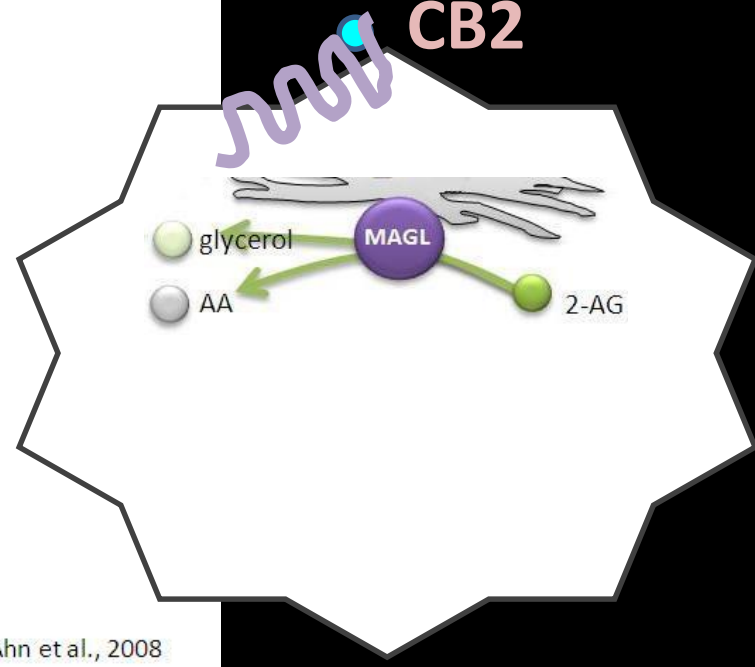
Chronic Pain

- Common clinical complaint
- Pathological (illness) or neuropathic (nerve damage/ inflammation)
- Light touch mechanical sensitivity (allodynia)
- Need for better therapeutics
- Combination of opioids and cannabinoids = enhanced effects

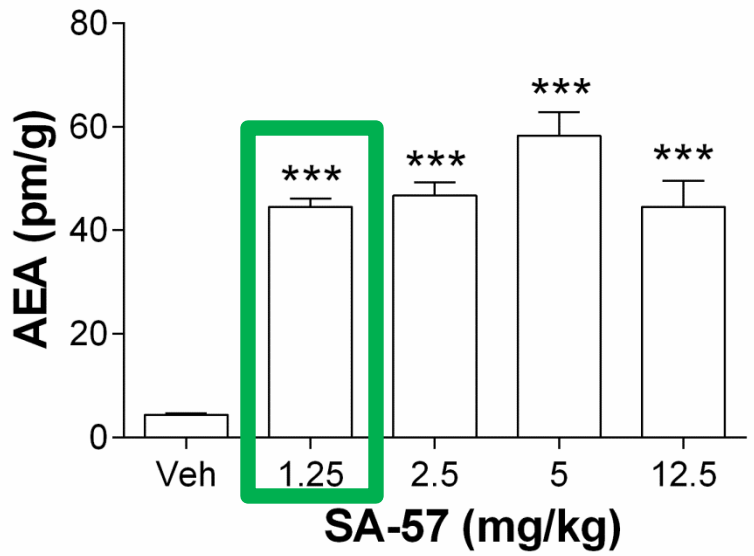
The Endocannabinoid System and Pain

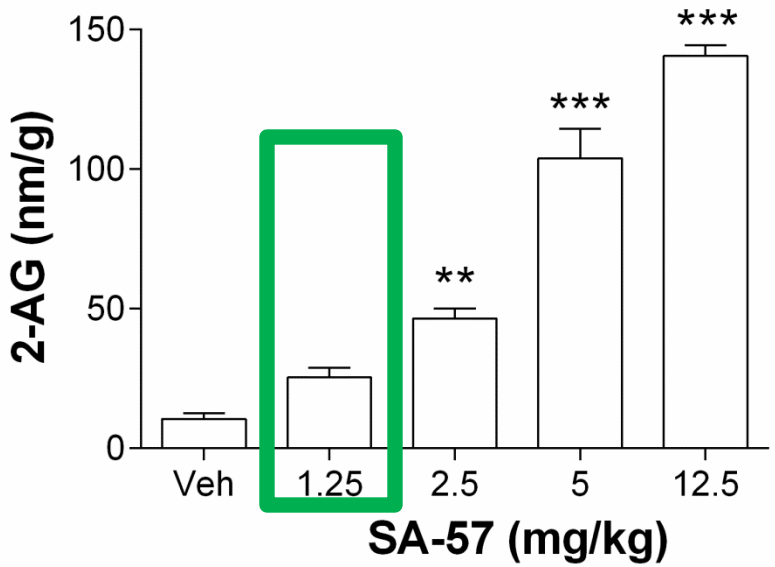


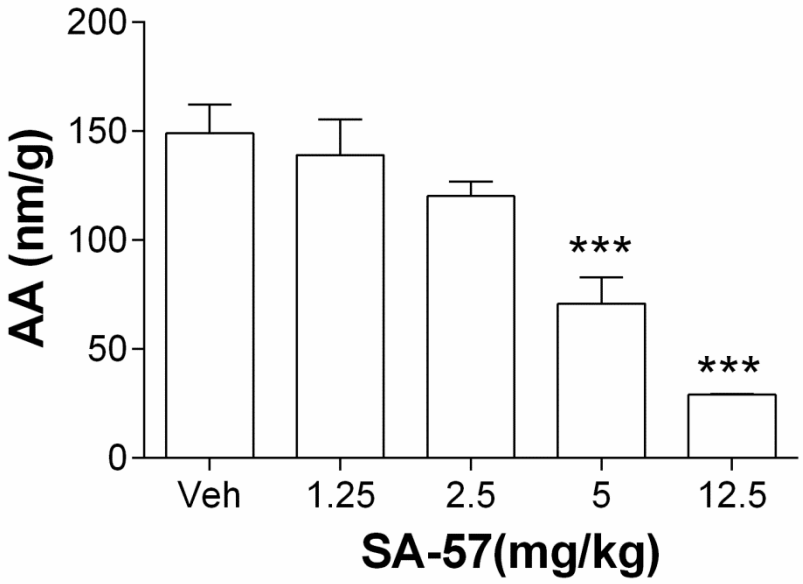
Immune Cells (microglia, macrophage)

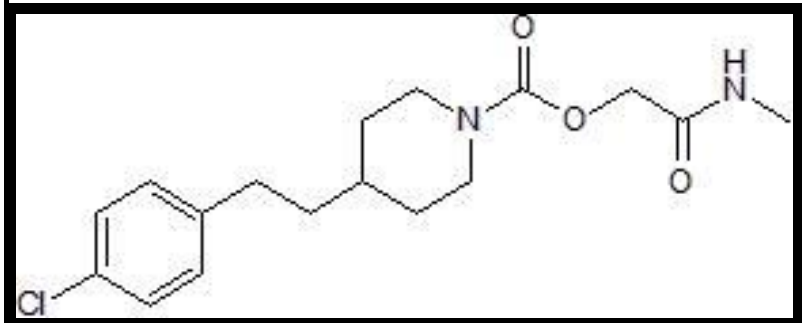


SA-57



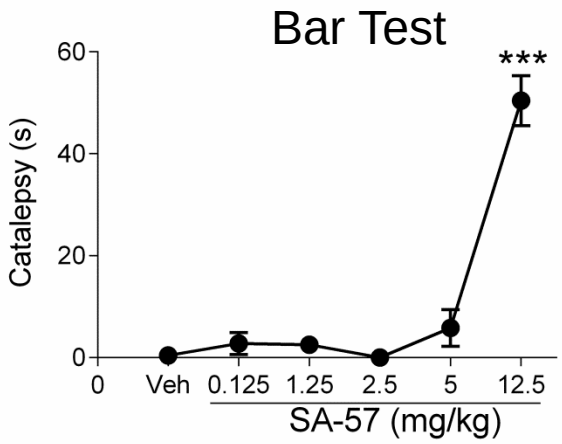


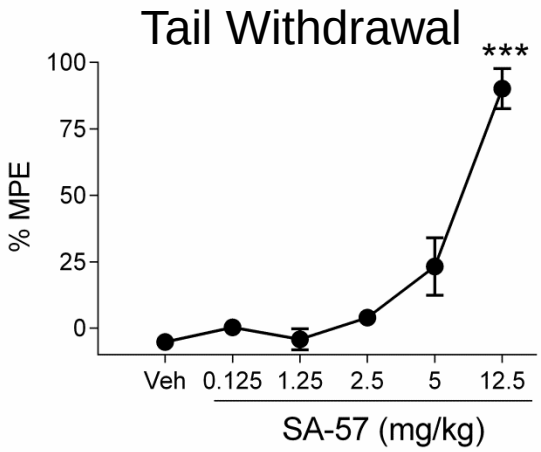


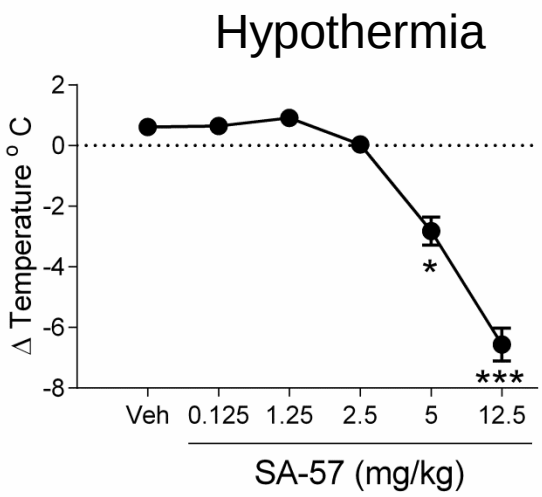


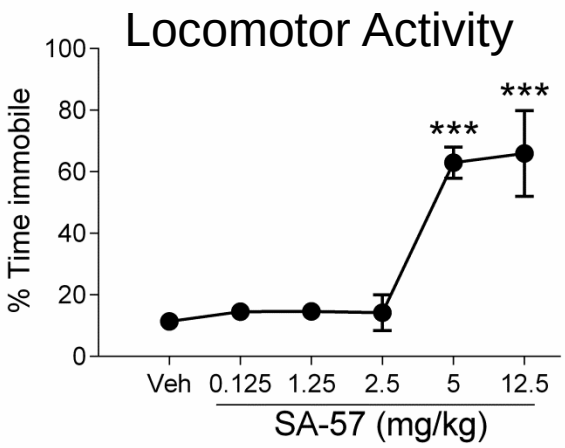
FAAH inhibition Ki = 1-3 nm
MAGL inhibition Ki = 410 nm
Brain Levels 2 h post i.p. administration
** = $p < 0.001$, *** = $p < 0.0001$ compared to Veh

High Doses of SA-57: Cannabimimetic Effects in the Tetrad









* = $p < 0.05$,
*** = $p < 0.0001$ compared to Veh

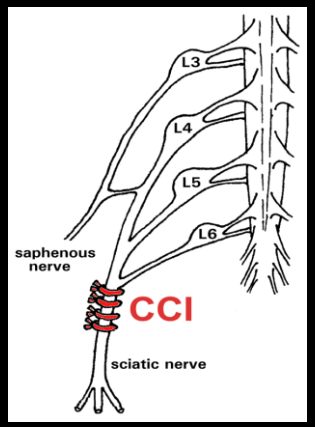
Hypothesis

“Dual inhibition of FAAH and MAGL will produce anti-allodynia in a mouse model of neuropathic pain, as well as opioid sparing effects.”

Neuropathic Pain

Chronic Constriction Injury (CCI)

- Model of neuropathic pain
- Isolate sciatic nerve
- Loose ligation with silk suture
- Inflammatory response, nerve trauma
- Sham surgery identical, except ligation

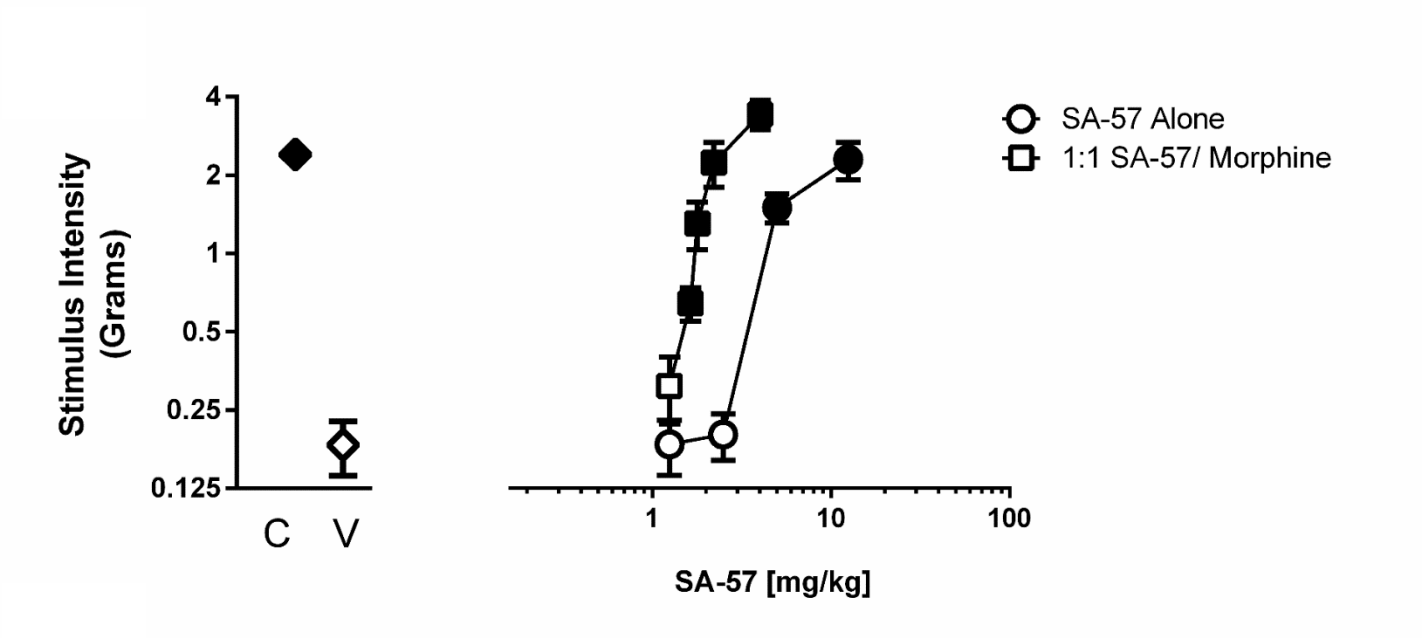


Bennett, GJ; Xie YK. (1988),Pain 33: 87-107

Allodynia

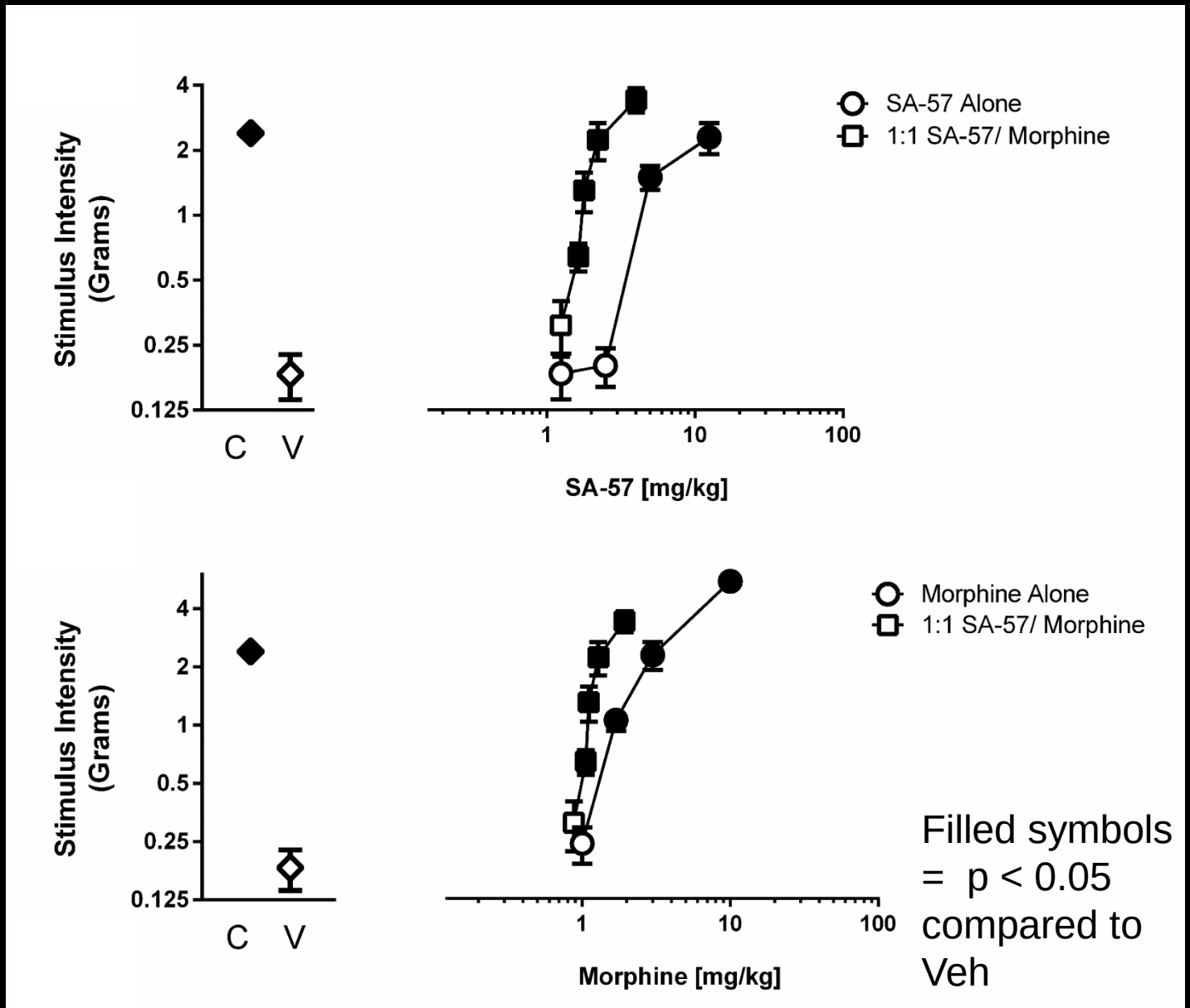
- Decrease in mechanical pressure threshold to produce response
- Assessed with calibrated thin monofilaments (von Frey) applied to hindpaw

SA-57 and Morphine: Shifting the Curve

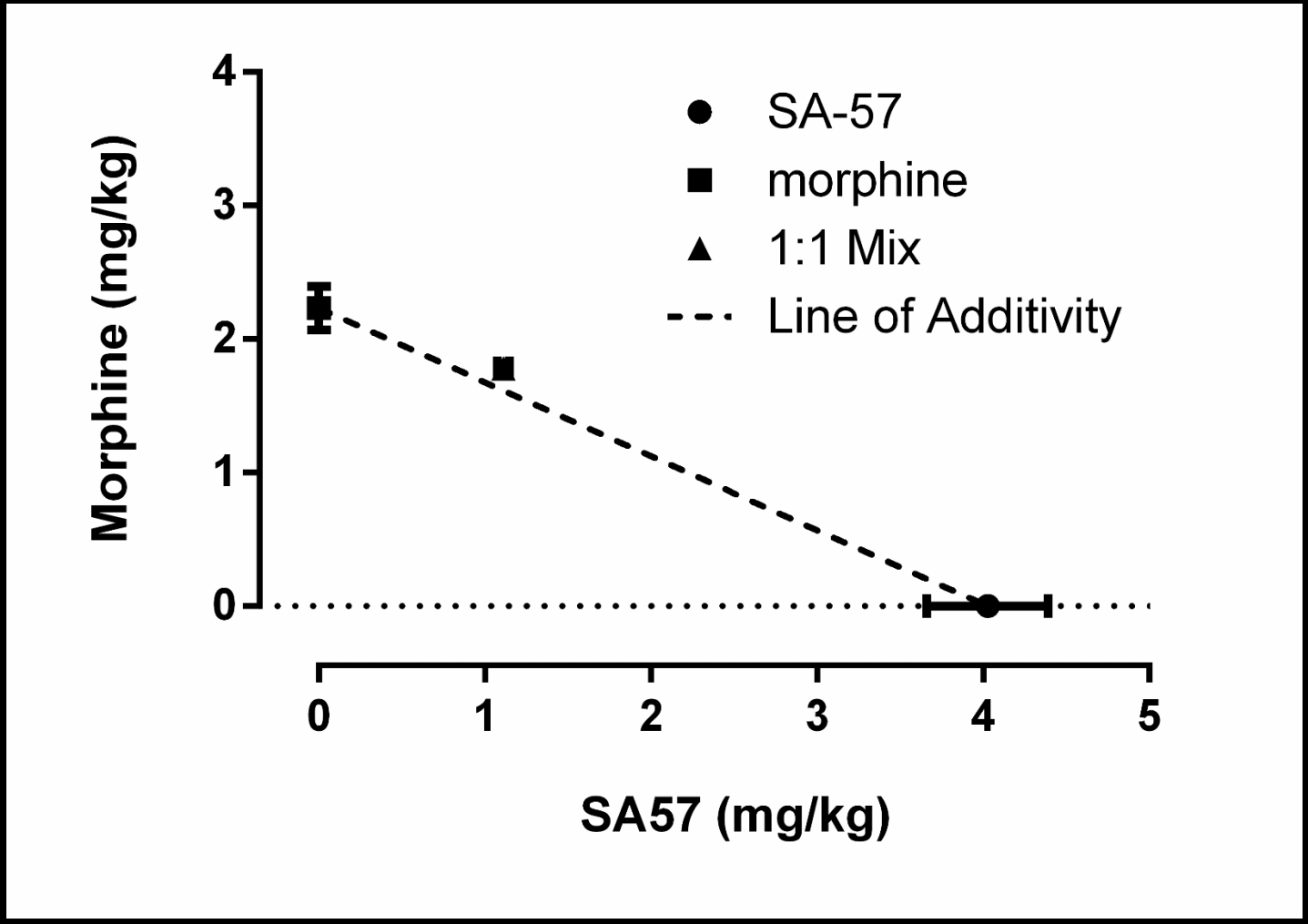


Filled symbols = $p < 0.05$ compared to Veh

SA-57 and Morphine: Shifting the Curve



SA-57 and Morphine: Additive Reversal of Allodynia

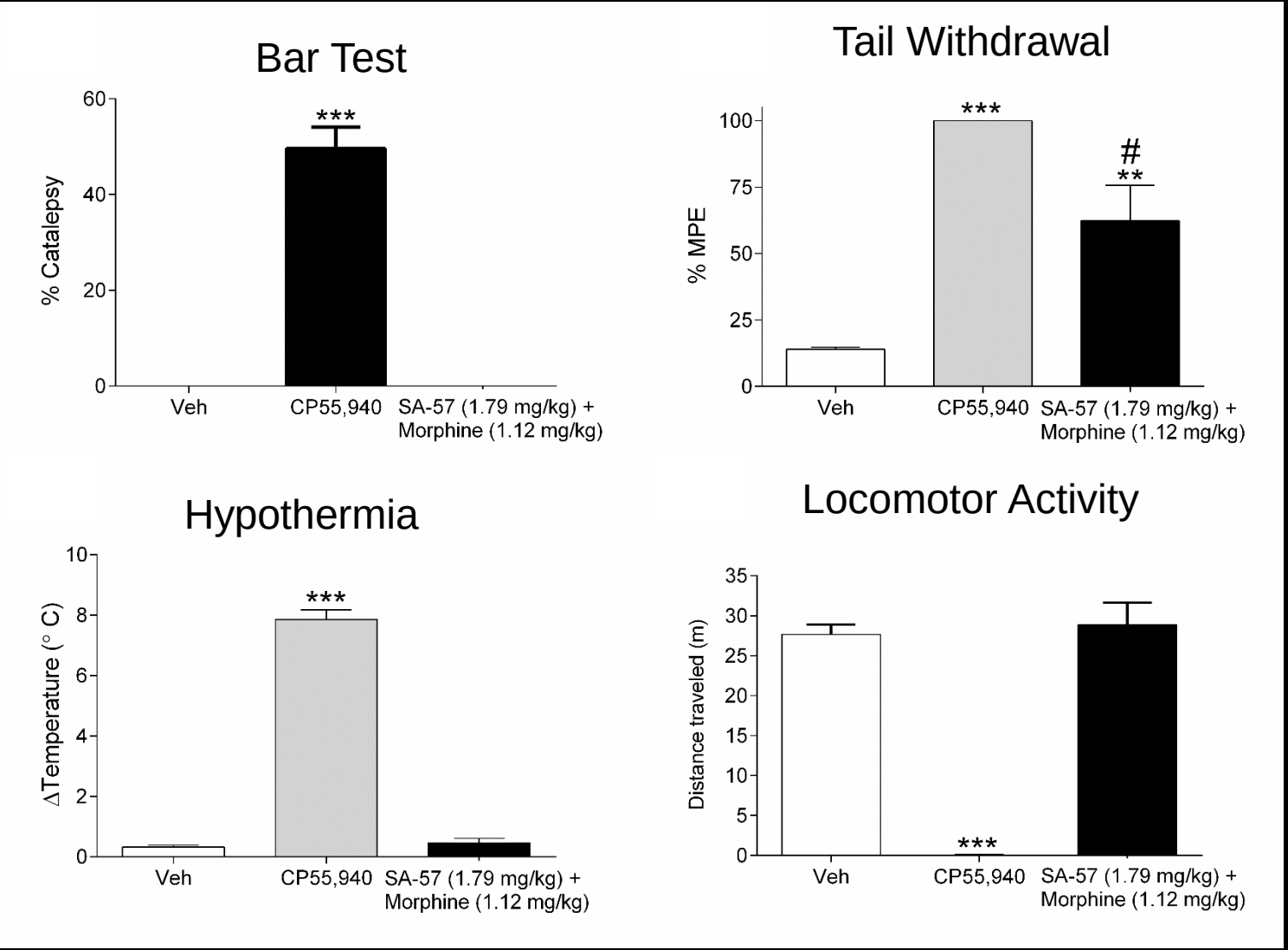


Combination of SA-57 and Morphine: Only Antinociceptive Tetrad Effect

1.79 mg/kg SA-57 + 1.12 mg/kg Morphine

(Pre-treatment time: SA-57 2 hr, Morphine 30 min)

** = p < 0.001
*** = p < 0.0001
Compared to veh
= p < 0.05
compared to CP55,940

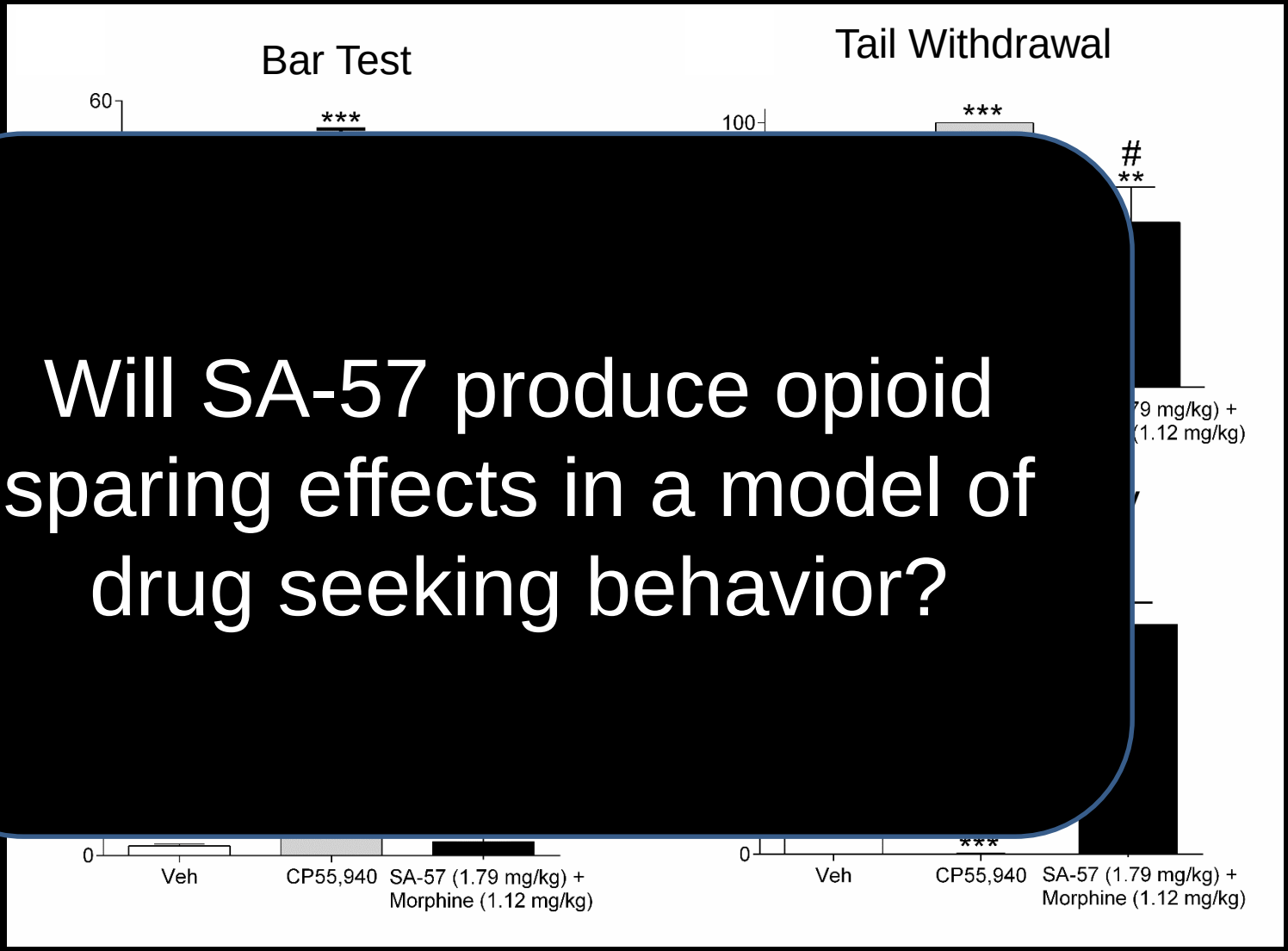


Combination of SA-57 and Morphine: Only Antinociceptive Tetrad Effect

1.79 mg/kg SA-57 + 1.12 mg/kg Morphine

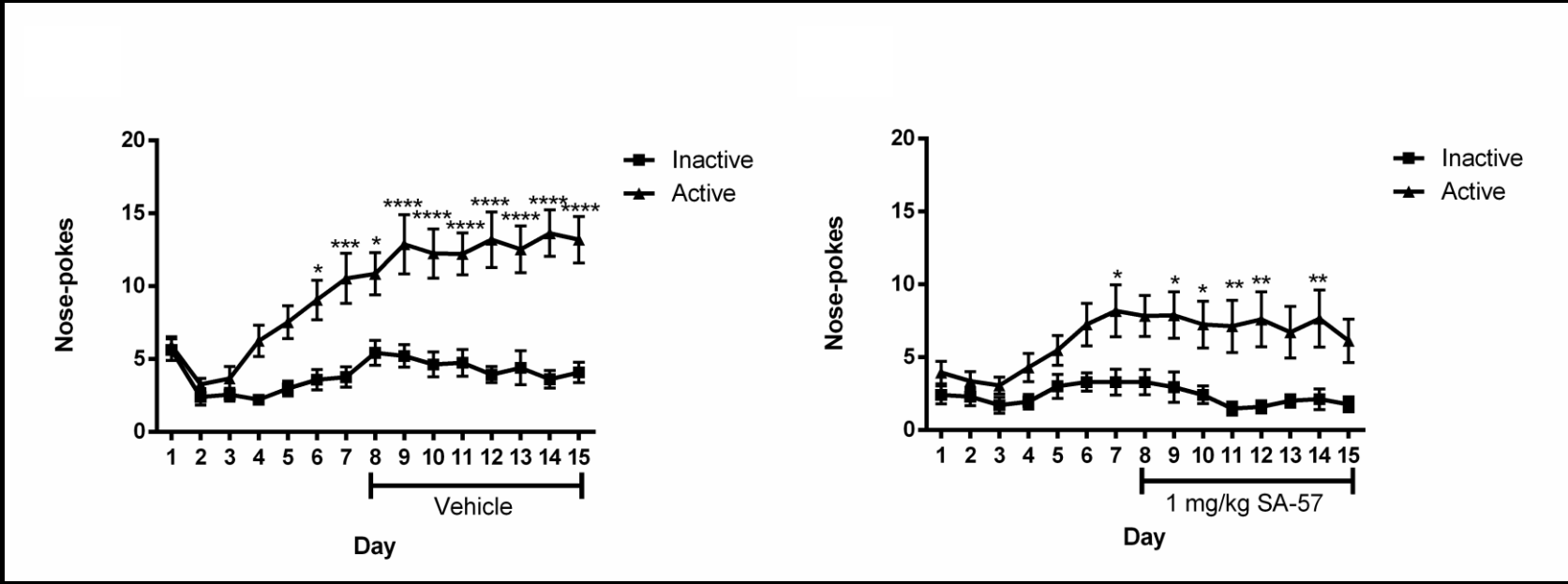
(Pre-treatme
time: SA-57
hr, Morphine
30 min)

** = p < 0.00
*** = p < 0.0(
Compared to
= p < 0.05
compared to
CP55,940

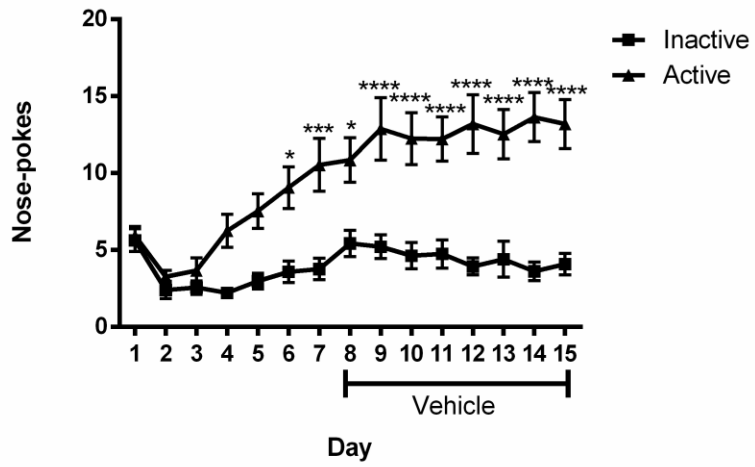


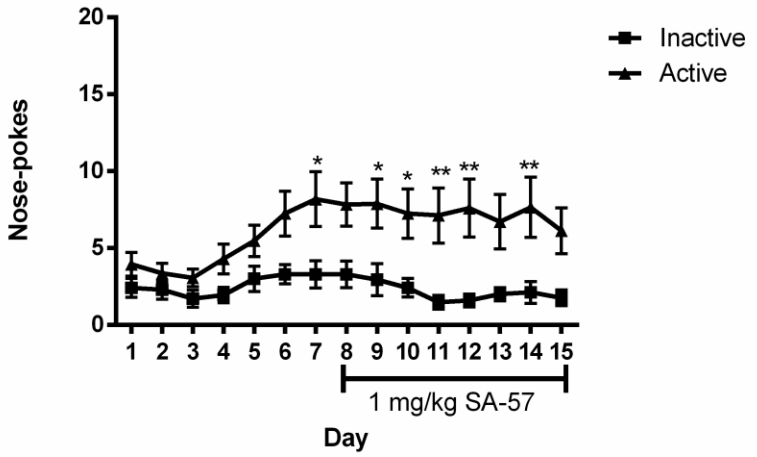
Will SA-57 produce opioid sparing effects in a model of drug seeking behavior?

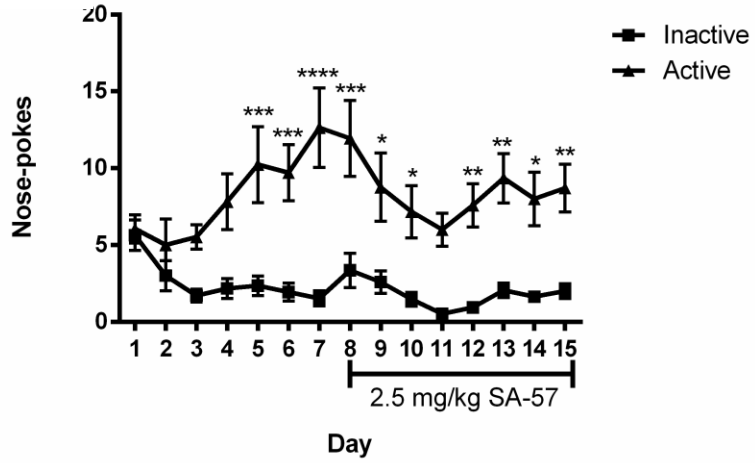
SA-57 Diminishes Heroin Seeking Behavior

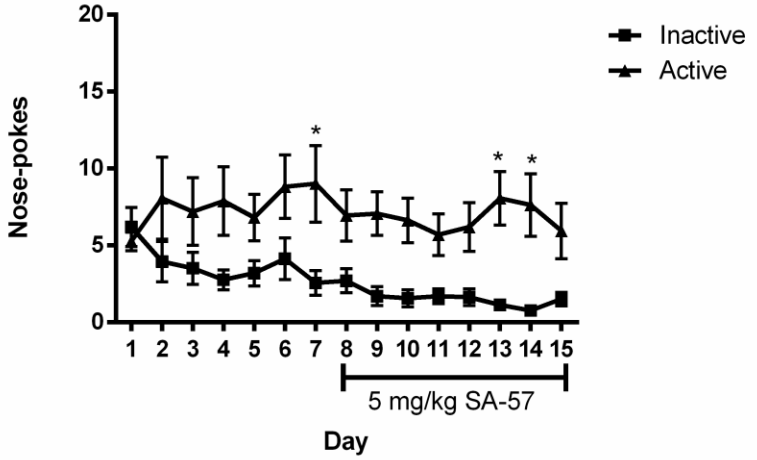


SA-57 Diminishes Heroin Seeking Behavior









Low Dose SA-57: FAAH Inhibition Sufficient, Translational Impact

The Pharmacogenomics Journal (2010) 10, 232–242

www.nature.com/tpj

ORIGINAL ARTICLE

Association of polymorphisms of the cannabinoid receptor (*CNR1*) and fatty acid amide hydrolase (*FAAH*) genes with heroin addiction: impact of long repeats of *CNR1*

D Proudnikov[1], T Kroslak[1], JC Sipe[2], M Randesi[1], D Li[3,4], S Hamon[3], A Ho[1], J Ott[3,5] and MJ Kreek[1]

A missense mutation in human fatty acid amide hydrolase associated with problem drug use

Jack C. Sipe*, Kyle Chiang, Alexandra L. Gerber, Ernest Beutler, and Benjamin F. Cravatt

The Skaggs Institute for Chemical Biology, and Departments of Molecular and Experimental Medicine, Chemistry, and Cell Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037

Contributed by Ernest Beutler, April 17, 2002

Summary and Conclusions

- SA-57: Narrow window between anti-allodynia and cannabimemetic effects

- Combination SA-57 and morphine:
  - Additive reversal of CCI-induced allodynia
  - Effective anti-allodynia without cannabimemetic effects

- SA-57 produces diminished heroin seeking behavior

- Endocannabinoid Catabolic Enzyme Inhibition= promising adjunct therapy to opioids for the treatment of neuropathic pain

Acknowledgements

- **Dr. Aron Lichtman (VCU)**
- **Dr. Benjamin Cravatt (TSRI)**
- **Dr. Rafael Maldonado (Spain)**

- **Funding**
  - **NIH Grants** DA009789, DA017259, F32DA038493