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

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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)

CB2

Presynaptic

Neurons

CB1

MAGL

glycerol

AA

2-AG

Postsynaptic

anandamide

ethanolamine

FAAH

AA

2-AG

Adapted from Ahn et al., 2008
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

**Allodynia**

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

Bennett, GJ; Xie YK. (1988), Pain 33: 87-107
SA-57 and Morphine: Shifting the Curve

Filled symbols = p < 0.05 compared to Veh
SA-57 and Morphine: Shifting the Curve

Filled symbols = \( p < 0.05 \) compared to Veh
SA-57 and Morphine: Additive Reversal of Allodynia

![Graph showing the relationship between SA57 and Morphine in mg/kg, with data points for SA-57, morphine, and a 1:1 Mix, along with a line of additivity.](image)
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
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Will SA-57 produce opioid sparing effects in a model of drug seeking behavior?
SA-57 Diminishes Heroin Seeking Behavior

![Graph showing the effect of SA-57 on Heroin Seeking Behavior](image)
SA-57 Diminishes Heroin Seeking Behavior

Graphs showing the number of nose-pokes over days for different doses of SA-57: Vehicle, 1 mg/kg SA-57, 2.5 mg/kg SA-57, and 5 mg/kg SA-57. Each graph compares inactive and active groups with statistical significance marked by asterisks.
Association of polymorphisms of the cannabinoid receptor (CNR1) and fatty acid amide hydrolase (FAAH) genes with heroin addiction: impact of long repeats of CNR1

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

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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
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