Sex-dependent antinociceptive effects of ACEA on acute inflammatory and chemotherapy-induced chronic pain models

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INTRODUCTION

Cannabinoid (CB) receptor agonists are emerging as promising therapeutic agents in the alleviation of inflammatory and chronic pain. CB receptor agonists modulate pain transmission by acting at G-protein coupled CB1 and CB2 receptors to activate the descending inhibitory pain pathways. Previous studies have shown that administration of the selective CB1 receptors agonist, arachidonyl-2-chloroethylamide (ACEA), results in anti-nociception in several rodent pain models and these anti-nociception effects of ACEA are sex-specific. In current study, we examine the dose and sex-dependent effects of ACEA on alleviating inflammatory and chemotherapy-induced pain in male and female wild-type mice.

METHODS

Acute Inflammatory Pain Model:

- Formalin test was used to investigate the dose (0.25, 0.5, 1 mg/kg) and sex-dependent analgesic effects of ACEA.
- ACEA was administered systemically via i.p. injection.
- Twenty minutes after the administration of ACEA, 10 µl of 2.5% formalin was injected into the hind paw of the mice.
- The level of behavioral indication of pain response was then observed for a one-hour time period, as seen in Figure 1.

Chronic Pain Model:

- Chemotherapeutic agent, cisplatin, was injected in male and female mice once a week for four weeks.
- On the eighth day of chemotherapy, ACEA or saline control was administered.
- Von Frey and acetone test were used to examine the effect of ACEA on alleviating mechanical and cold allodynia, respectively.
- Estrous cycles of the female mice were monitored daily throughout the cisplatin-induced neuropathic pain study to investigate the potential influence of ACEA on estrous cycles.

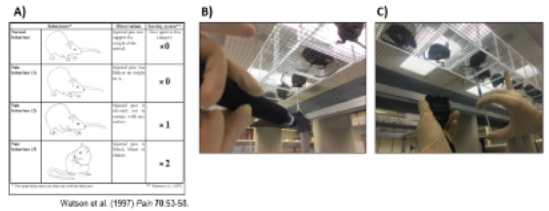

Figure 1. Formalin test, Von Frey test, and acetone test were used to examine the effect of ACEA on the inflammatory and chronic pain in this study. (A) In formalin test, behavioral indication of pain was observed throughout one hour time period. (B-C) Photo illustration of Von Frey and acetone test.

RESULTS

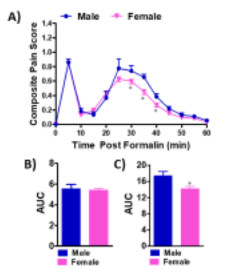

Figure 2. WT mice' sensitive to pain in the formalin test. (A-C) Male and female mice experienced equal sensitivity to pain in the acute phase (B), but female mice' sensitivity to pain was significant lower in the inflammatory pain phase compared to male mice (C).

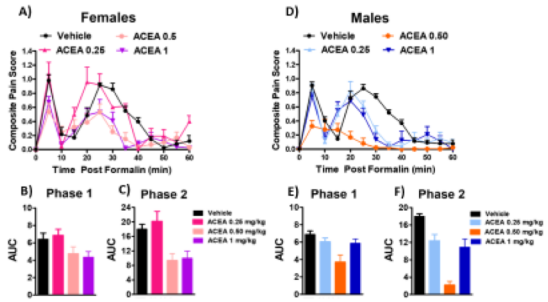

Figure 3. Male and female mice demonstrated distinct dose-dependent responses to ACEA-induced alleviation of inflammatory pain. (A-C) Female mice showed lower pain sensitivity when treated with 0.5 or 1.0 mg/kg of ACEA compared to the administration of 0.25 mg/kg of ACEA . (D-F) Male mice only showed lower pain sensitivity when treated with 0.5 mg/kg of ACEA but not 0.25 or 1.0 mg/kg of ACEA.

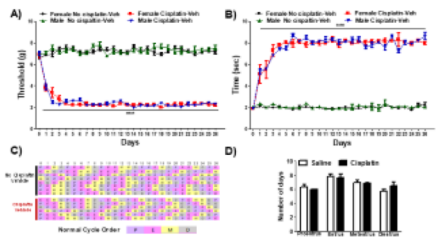

Figure 4. Cisplatin induced equal trends in neuropathic pain in both male and female mice and cisplatin treated female mice showed no disruptions to their estrous cycles. Results from Von Frey (A) and acetone (B) test indicated that cisplatin induced neuropathic pain in both sexes. (C-D) No significant interference in estrous cycles was observed between saline treated or cisplatin treated female mice.

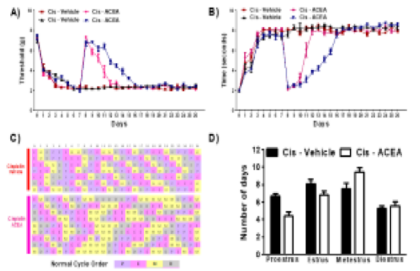

Figure 5. Systemic administration of ACEA suppressed the cisplatin-induced chronic pain in both sexes and disrupted the estrous cycles in ACEA treated female mice. Administration of ACEA via i.p. route on the eighth day of chemotherapy increased the pressure threshold in Von Frey (A) test and decreased the required time to respond to acetone (B) test. (C-D) Compared to cisplatin treated female mice that received vehicle control injection, cisplatin treated female mice underwent ACEA treatment showed irregular estrous cycles.

SUMMARY

In the inflammatory pain model:

- Comparable sensitivity to formalin-induced pain was observed in both sexes in the acute phase. Significant lower sensitivity to pain was found in only females in the inflammatory pain phase.
- ACEA showed sex and dose-dependent antinociceptive effects.

In the cisplatin-induced chronic pain model:

- ACEA reduced mechanical and cold allodynia in both sexes.
- Females developed tolerance faster than males to ACEA.
- ACEA treatment resulted in irregular estrous cycles, suggesting that endocannabinoid systems might interact with sex hormone signaling pathways.

ACKNOWLEDGEMENTS

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NIH National Institute on Drug Abuse Advancing Addiction Science

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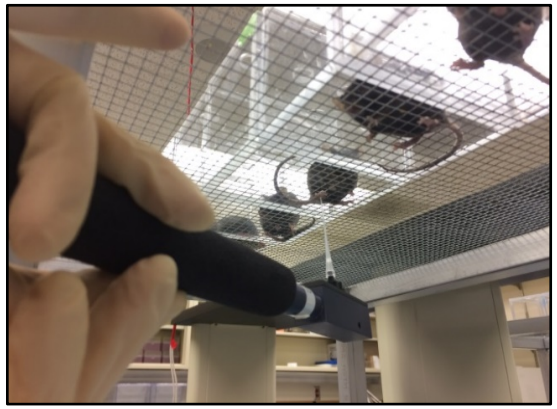
A)

Behaviours*		Observations	Scoring system**
Normal behaviour		Injected paw can support the weight of the animal.	Time spent in this category **× 0**
Pain behaviour (1)		Injected paw has little or no weight on it.	**× 0**
Pain behaviour (2)		Injected paw is elevated, not in contact with any surface.	**× 1**
Pain behaviour (3)		Injected paw is licked, bitten or shaken.	**× 2**

* The same behaviours are observed with the hind paw. ** Watson *et al.* (1997)

Watson et al. (1997) *Pain* **70**:53-58.

B)



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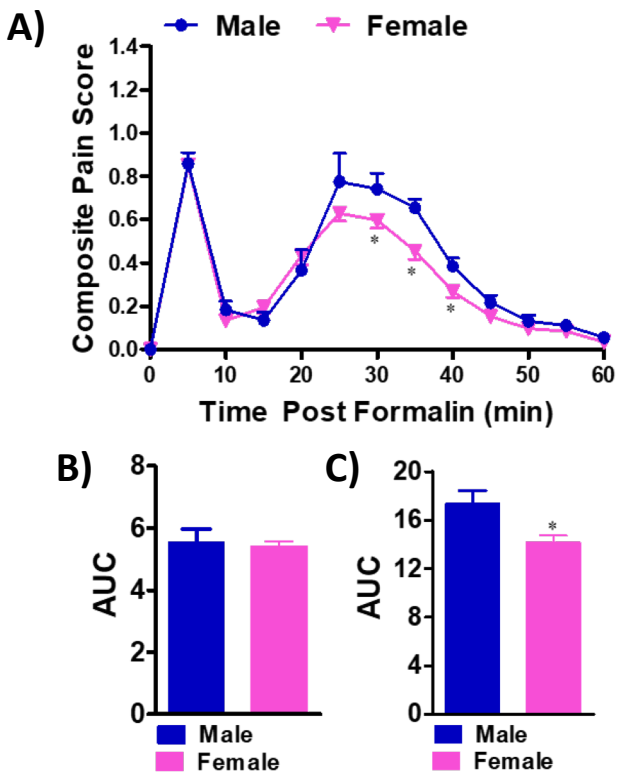

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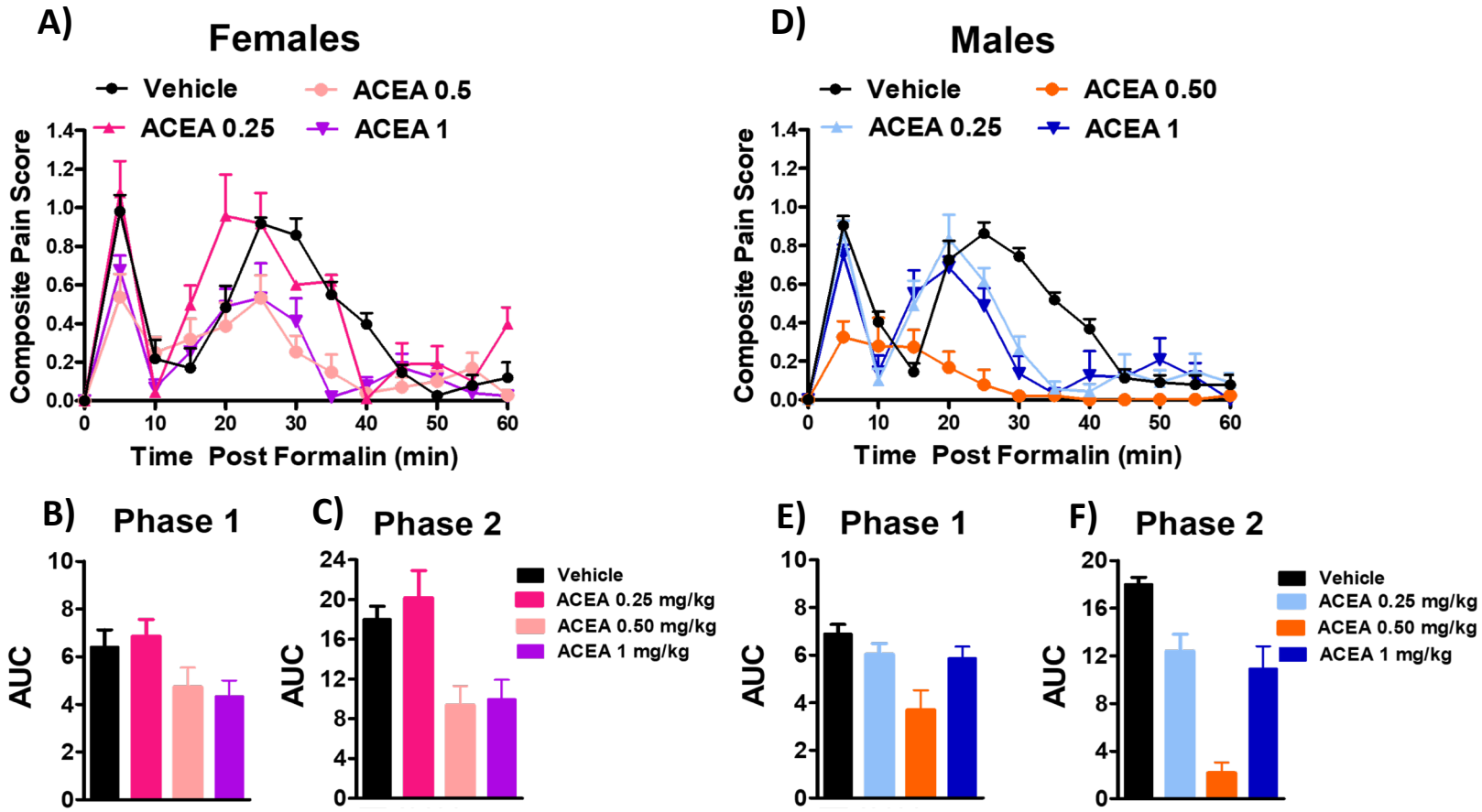

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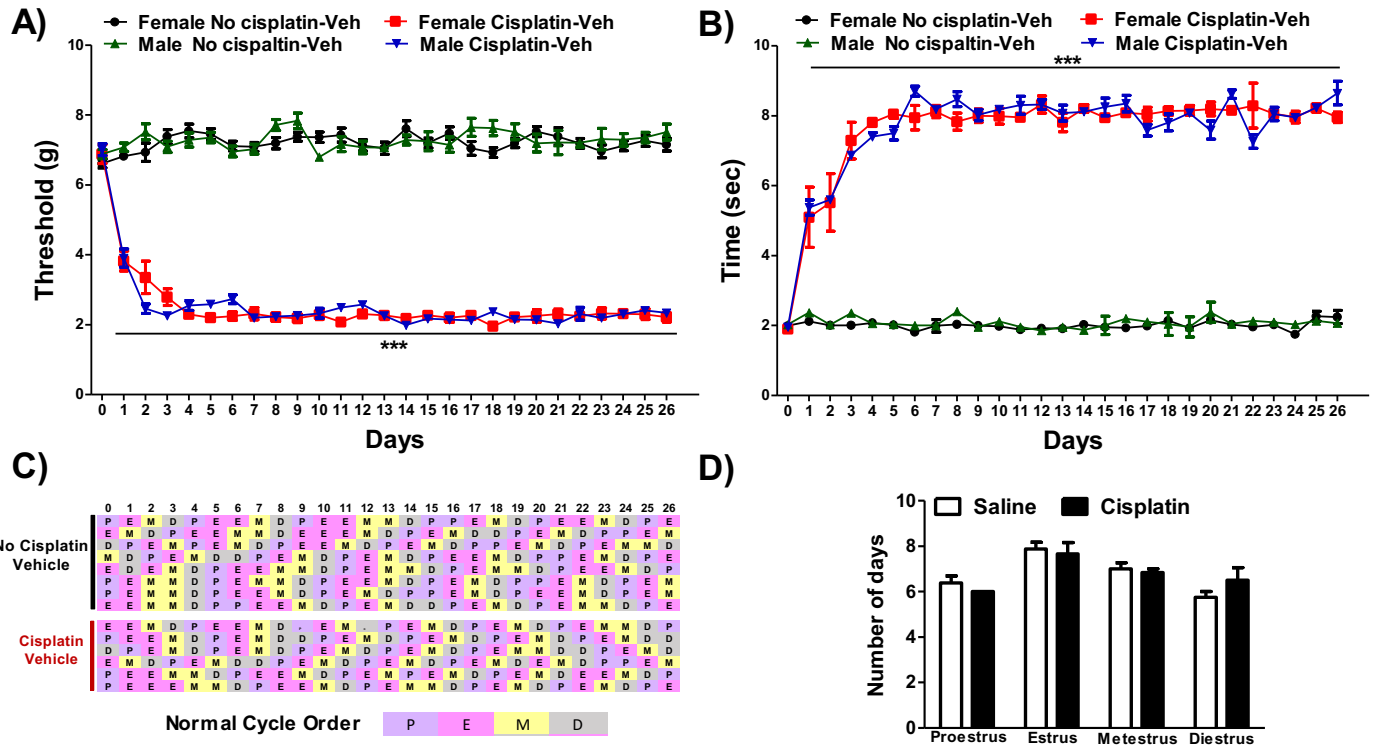

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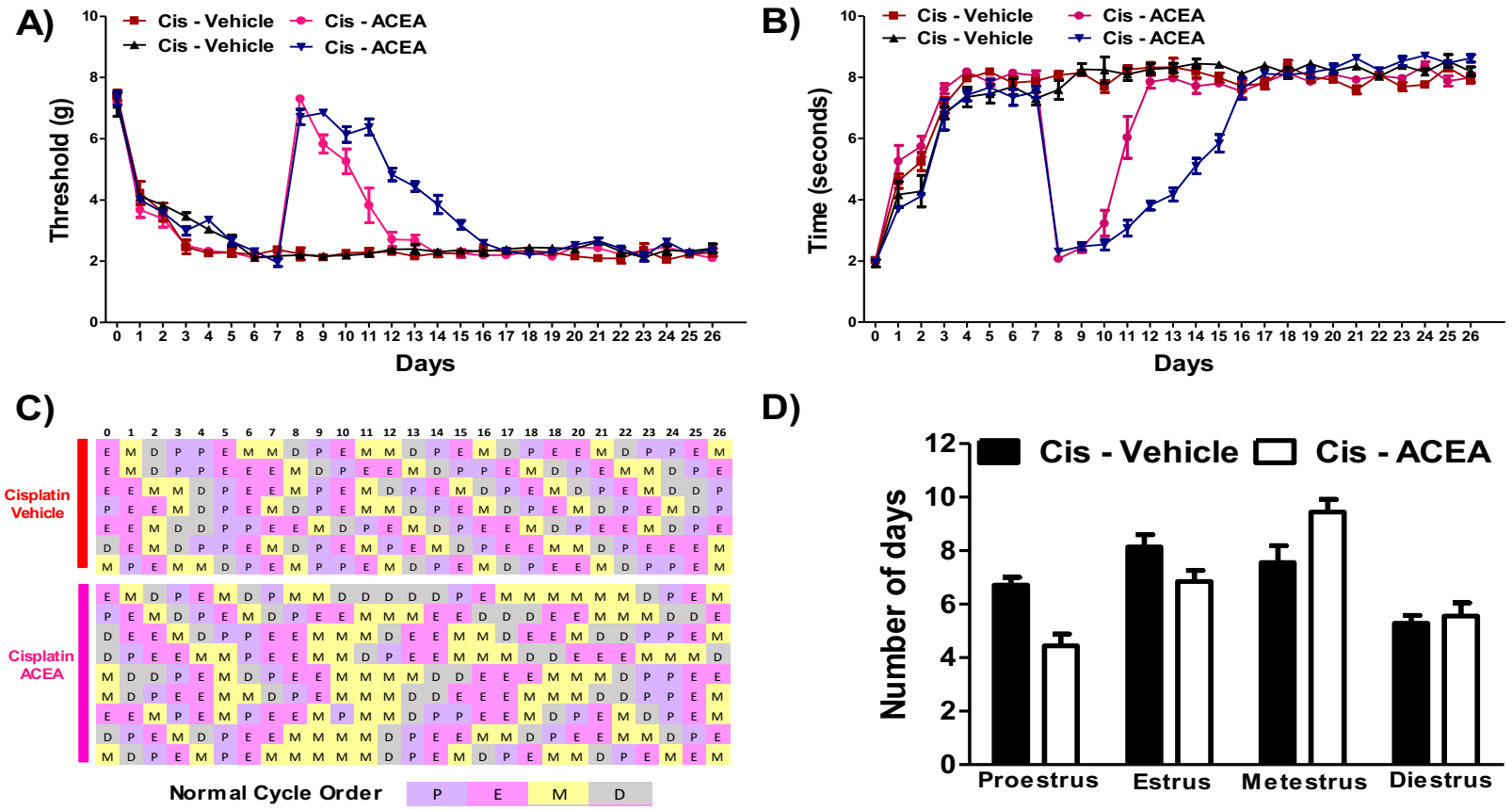

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