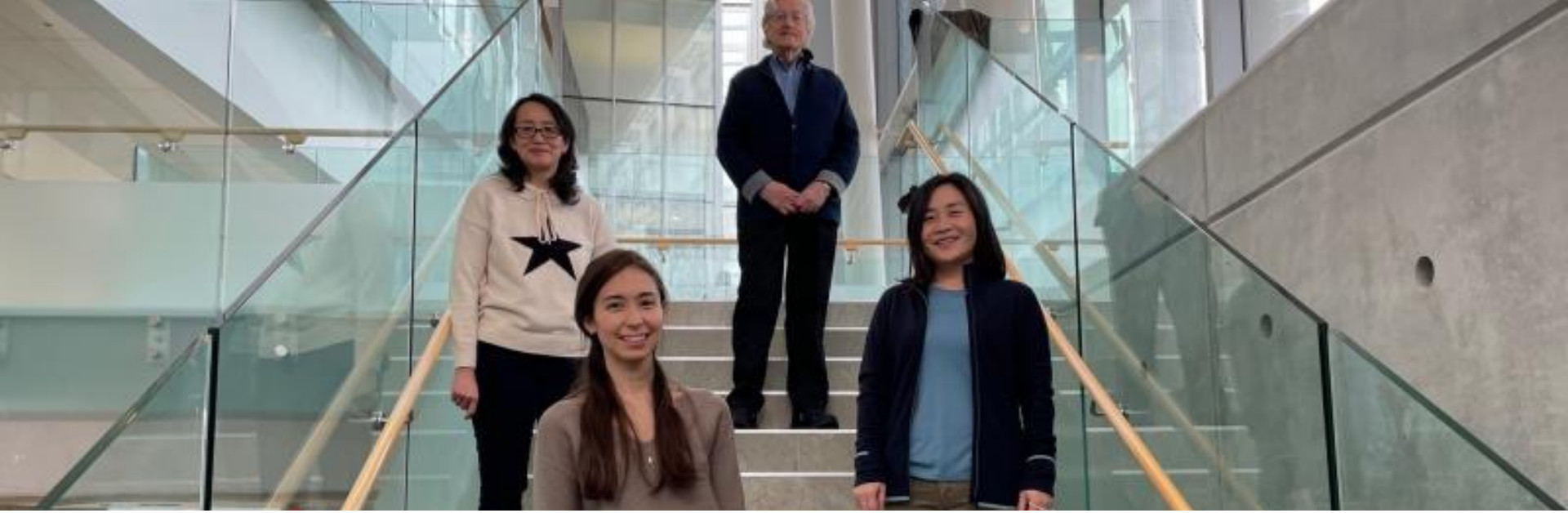

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Neural bases for attenuation of morphine withdrawal by Heantos-4: role of *l*-tetrahydropalmatine

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Competing interests

- A.G.P. holds a US patent entitled “Tetrahydroprotoberbine Compounds and Uses Thereof” in the Treatment of Neurological, Psychiatric and Neurodegenerative Diseases. United States. US20150306092.
- A.G.P. also holds shares in Resilience Biosciences Inc., Canada., focused on tetrahydroprotoberberine drug development.

Outline of Presentation

- Highlight recent preclinical studies from the Phillips lab at UBC that have revealed both a **Mechanism of Action** and a **Biological Signature** with which to characterize the effects of the botanical formulation **Heantos-4** as an aid in the treatment of opioid detoxification.
- Identify an active molecule called ***l*-tetrahydropalmatine** (***l*-THP**) from amongst the 194 chemical classes that comprise the **Heantos-4** formulation, which has similar neurochemical and pharmacological properties as **Heantos-4**.
- Could ***l*-THP** also be a promising candidate for facilitating withdrawal from dependence on opioids**?**

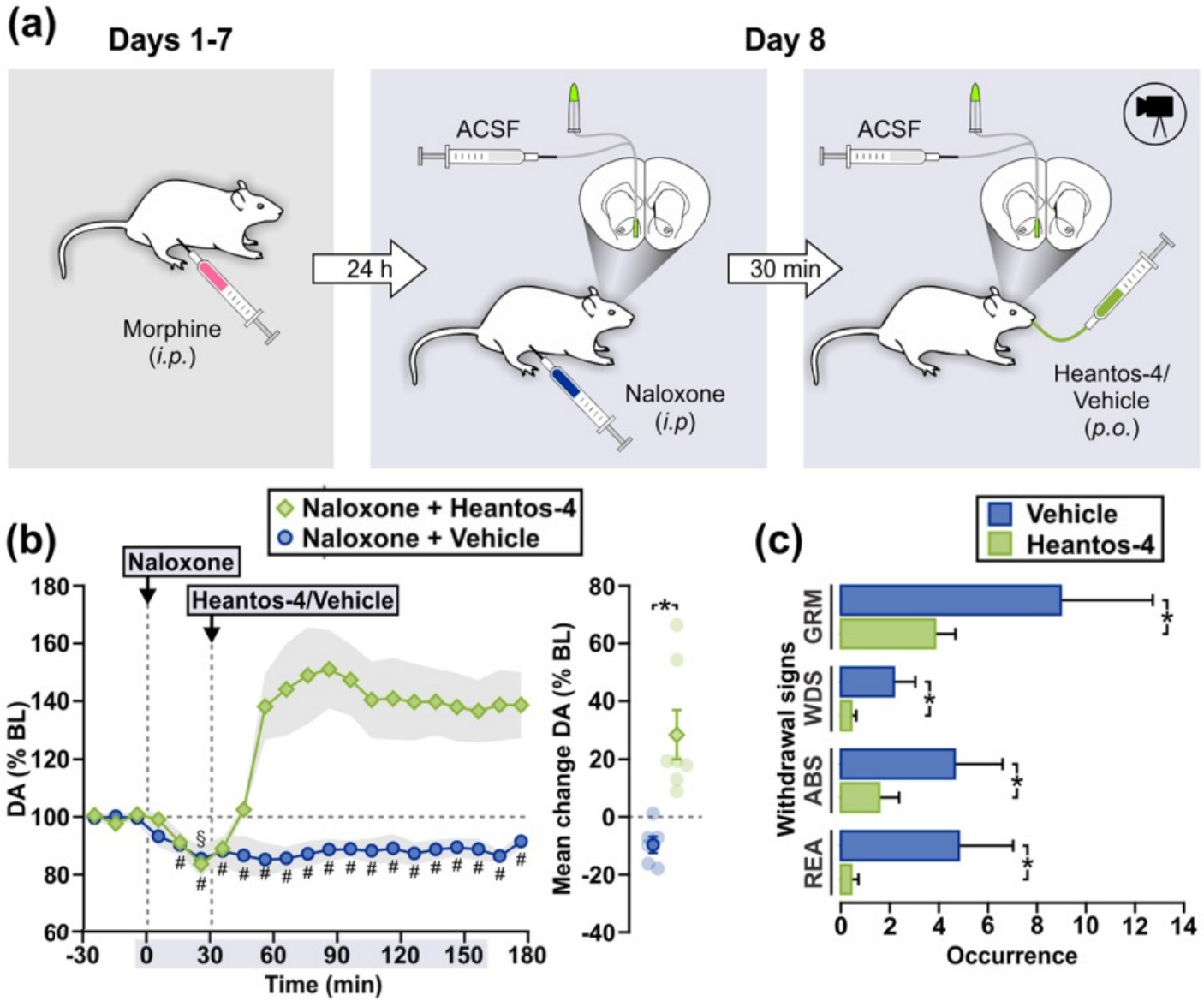

Figure 1. Heantos-4 stimulates DA efflux from a hypodopaminergic state and alleviates somatic withdrawal signs in morphine-dependent rats.

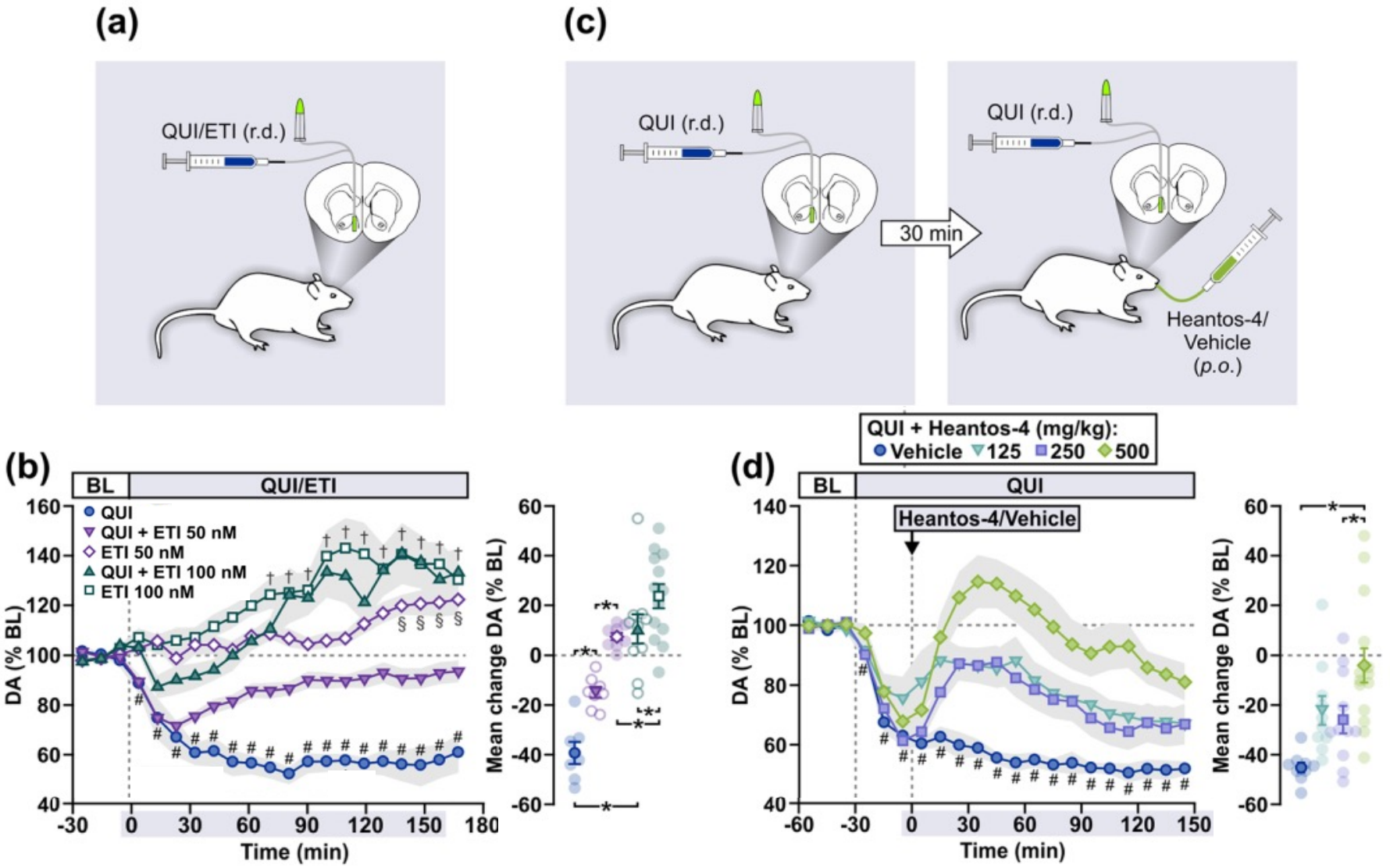

Figure 2. Heantos-4 reverses DA autoreceptor-mediated inhibition of DA efflux.

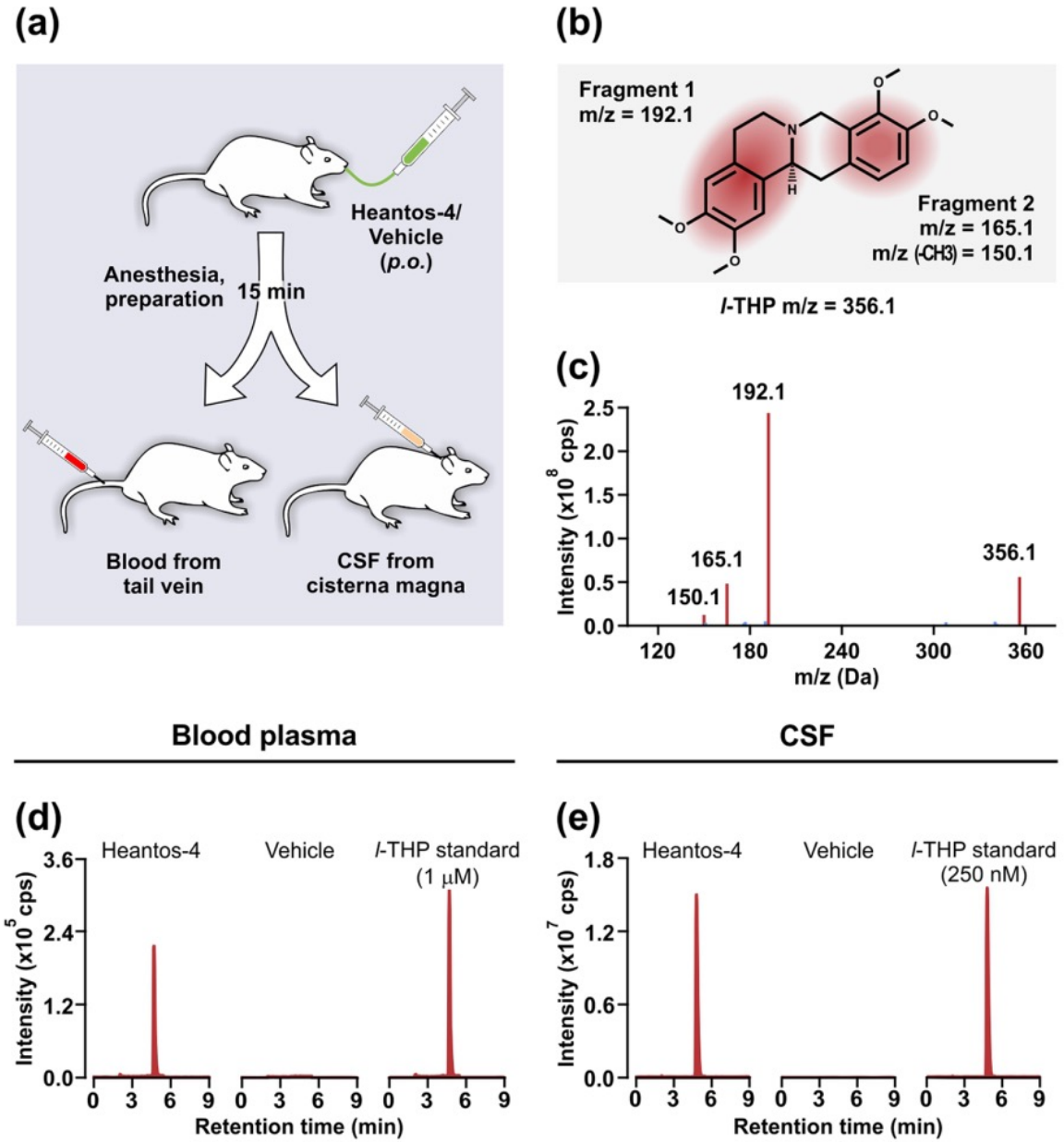

Figure 3. *l*-THP is detected in blood plasma and cerebrospinal (CSF) following oral Heantos-4.

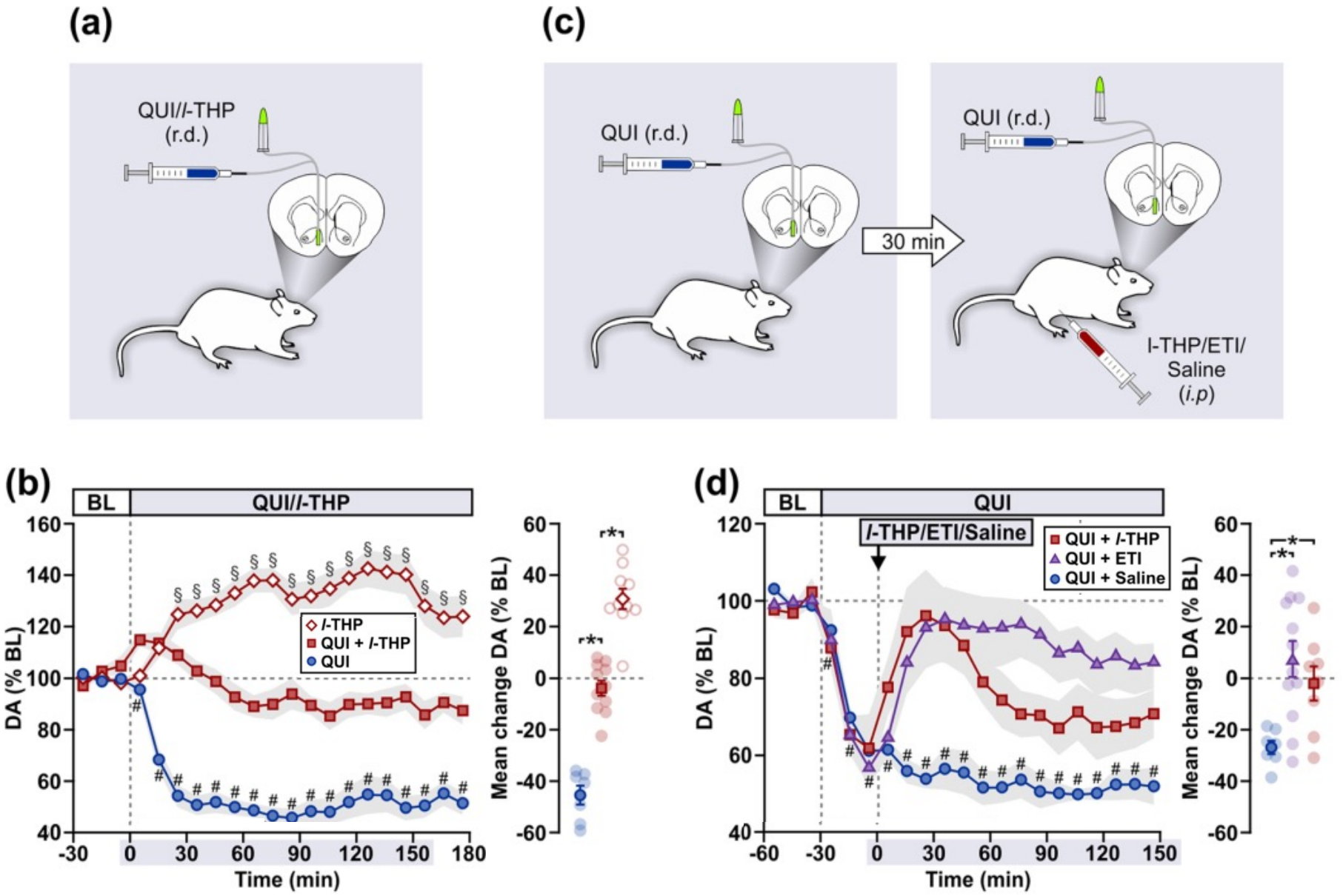

Figure 4. */*-THP reverses DA autoreceptor-mediated inhibition of DA efflux.

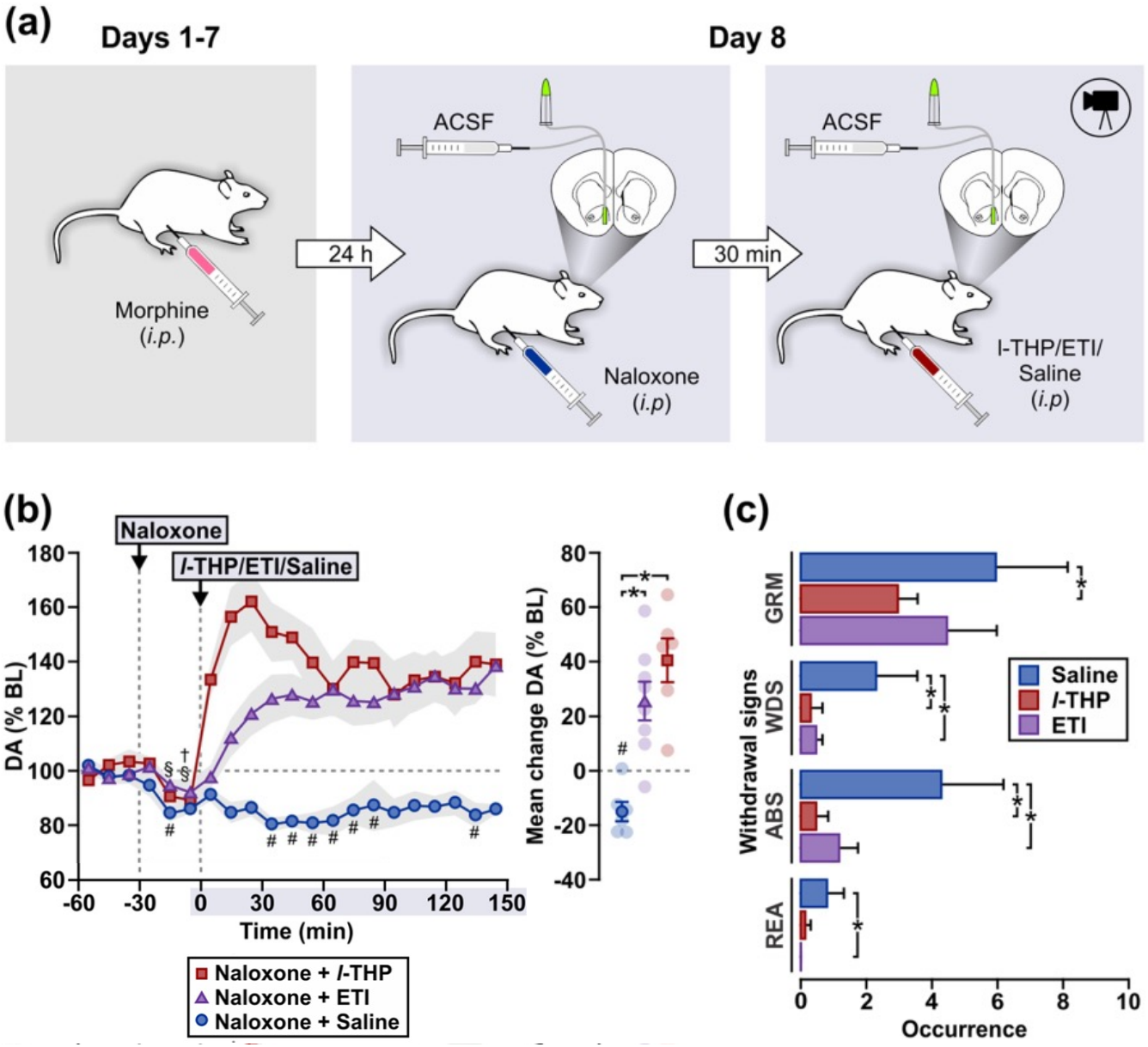

Figure 5. *l*-THP stimulates DA efflux from a hypodopaminergic state and alleviates somatic withdrawal signs in morphine-dependent rats.

Summary and Conclusions

- Oral administration of the botanical formulation **Heantos-4** AFTER treatment with naloxone **reverses Hypo-Dopaminergia** and **significantly reduces the severity of withdrawal signs.**
- **Hypo-Dopaminergia** is attributed to enhanced activation of the inhibitory pre-synaptic dopamine-autoreceptor, induced by either quinperole a dopamine agonist, OR by oral administration of **Heantos-4** . Accordingly, these data provide a **Mechanism of Action** that may explain both the reversal of **Hypo-Dopaminergia** and **facilitated withdrawal in opioid-dependent rats**.
- Of equal importance, our UHPLC/MS/MS analyses of plasma and brain-CSF following oral administration of **Heantos-4** revealed the presence of ***l*-THP** a compound under active investigation in addiction medicine. In the present context, ***l*-THP** provides a **Biological Signature** with which to perform PK/PD studies of Heantos-4.
- A final experiment confirmed that systemic administration **of *l*-THP could recapitulate both the reversal of Hypo-Dopaminergia and reduction of withdrawal signs** induced by naloxone in morphine-dependent rats.
- Together, these preclinical findings provide a strong biological foundation for the use of the **Heantos-4** botanical formulation that compliments its clinical use as a supplement during detoxification from both acute or chronic dependence on opioids.