Phyto-cannabinoids Inhibits Peripheral Nociceptors by Targeting Sodium Channels

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Background

Phyto-cannabinoids, natural compounds from *Cannabis sativa*, have attracted growing interest for their therapeutic potential across various conditions, including chronic pain, inflammation, epilepsy, sleep disorders, psychiatric illnesses, and metabolic dysfunctions. Despite extensive use, the molecular mechanisms by which cannabinoids exert their effects remain incompletely understood.

The peripheral cannabinoid hypothesis suggests that cannabinoid receptors outside the central nervous system, particularly on sensory neurons, play a significant role in mediating analgesic and anti-inflammatory effects. This peripheral targeting may allow effective pain relief without central side effects like sedation or cognitive impairment.

A key focus of current research is the interaction between phyto-cannabinoids and voltage-gated sodium (NaV) channels, which are essential for neuronal excitability and pain signalling. Recent studies show that cannabinoids modulate NaV channel activity, reducing nociceptor excitability and contributing to analgesia. However, the molecular mechanisms and the diversity of cannabinoid effects on various NaV subtypes remain poorly defined.

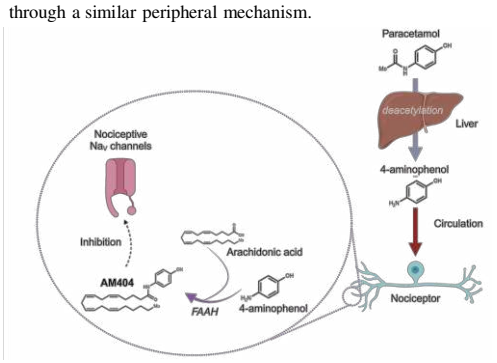
Methods

We characterized the pharmacological effect of the major phyto-cannabinoids on nociceptors from the trigeminal ganglion (TG) using both voltage- and current-clamp recordings. To specifically define the mechanism of phyto-cannabinoids on pain pathway-related Nav channels, we expressed human Nav channels in HEK and ND7/23 cells and characterized the biophysical properties of the phyto-cannabinoids' current modulation.

Purpose and Hypothesis

In our recent study, we demonstrated that AM404, a cannabinoid-related metabolite of paracetamol, acts peripherally to inhibit pain-related sodium channels directly[1].

We also found that the psychoactive Δ^9-tetrahydrocannabinol (THC) inhibit nociceptors' firing[2]. Based on this, we hypothesize that phyto-cannabinoids produce analgesia through a similar peripheral mechanism.



The scheme depicting the "peripheral hypothesis" AM404 mechanism of action.

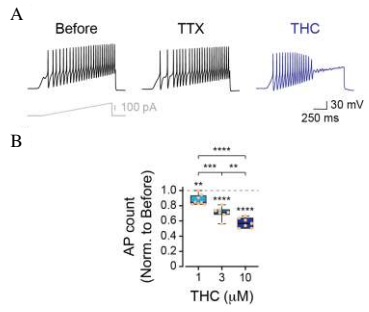
Researching how phyto-cannabinoids interact with NaV channels and peripheral targets is vital for developing safer, non-opioid pain therapies.

By targeting peripheral pathways rather than the central nervous system, these compounds offer a route to pain relief that avoids the addiction and dependency risks common with traditional treatments.

Ultimately, this work informs drug development strategies aimed at treating chronic pain and inflammation without the burden of substance use disorders.

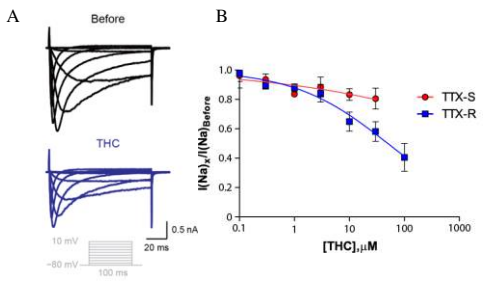
Results

THC inhibits nociceptive firing in a dose-dependent manner



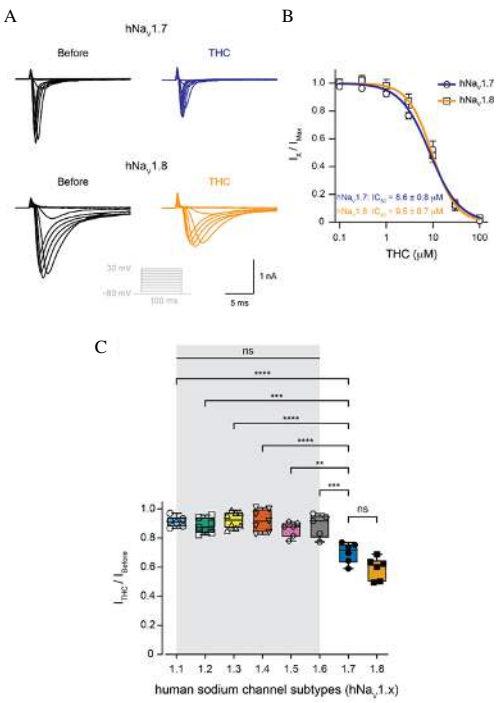
THC inhibits nociceptive firing. A. Representative whole-cell current-clamp recording from acutely dissociated rat nociceptive TG neurons in response to a current ramp before (left), during exposure to 0.1 μM TTX (middle), and during exposure to 10 μM THC (right). **B.** Concentration-response relationship for inhibition of the action potentials firing by THC in nociceptor TG neurons. One-way ANOVA, followed by Bonferroni's post hoc test when **, $p \leq 0.01$; ***, $p \leq 0.001$; ****, $p \leq 0.0001$.

In nociceptor neurons, THC preferentially inhibits TTX-R sodium currents



THC inhibits nociceptive sodium currents. A. Representative whole-cell voltage-clamp traces of TTX-R sodium currents in dissociated rat TG neurons before (top) and after 10 μM THC (bottom). **B.** Concentration-response curve of normalized TTX-R (blue) and TTX-S (red) current amplitudes after THC exposure; the solid line indicates a Hill equation fit.

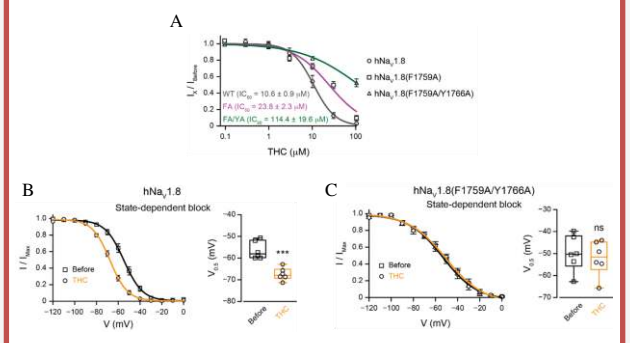
THC selectively inhibits nociceptive sodium channels



THC selectively inhibits the nociceptive hNaV1.8 and hNaV1.7 channels. A. Representative whole-cell voltage-clamp traces of hNaV1.7 (HEK293T cells; top) and hNaV1.8 (ND7/23 cells; bottom) before (left) and after 10 μM THC (right). **B.** Concentration-response curves for THC inhibition of hNaV1.7 (circles) and hNaV1.8 (squares). Data points represent mean ± SEM (n≥6). **C.** Peak current inhibition of various hNaV channels by 10 μM THC.

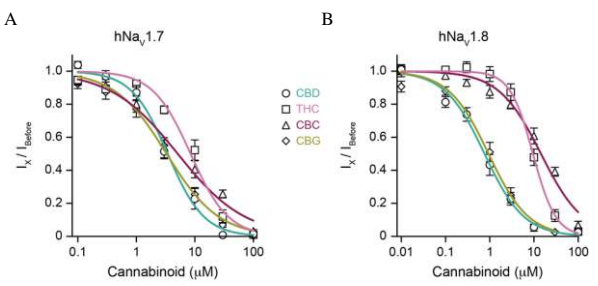
Results

THC inhibits nociceptive sodium channels via the local anesthetic binding site



THC exerts its inhibitory effect on nociceptive sodium channels by targeting the local anesthetic binding site A. Concentration-response curves for THC inhibition of wild-type (WT), F1759A (FA), and F1759A/Y1766A (FA/YA) hNaV1.8 channels. The substantial rightward shift for both mutants indicates a significant loss of inhibitory potency compared to WT. **B.** hNaV1.8 steady-state availability. Left: Normalized current (I/I_{max}) vs. conditioning voltage before (squares) and after THC (circles). Right: $V_{0.5}$ values showing a significant hyperpolarizing shift, indicating THC stabilizes the inactivated state. Paired Student's *t*-test when ***, $p \leq 0.001$. **C.** Same as (B), but recorded from cells expressing the double mutant hNaV1.8(F1759A/Y1766A) channel. Note that the mutations abolish the THC-induced shift in voltage-dependent inactivation, demonstrating a loss of state-dependent block. Paired Student's t-test when ns, not significant.

Nociceptive sodium channels exhibit differential sensitivity to phyto-cannabinoids



hNaV1.8, but not hNaV1.7, has a different susceptibility to phyto-cannabinoids. Concentration-response curves for hNaV1.7 (A) and hNaV1.8 (B) inhibition by CBD (circles), THC (squares), CBC (triangles), and CBG (diamonds). Peak currents are plotted against cannabinoid concentration and fitted to the Hill equation. Data represent mean ± SEM (n≥6).

Conclusions

- **Direct Sodium Channel Inhibition:** THC directly targets and inhibits the voltage-gated sodium channels NaV1.7 and NaV1.8, which are critical for pain signaling in peripheral nociceptors.
- **Local Anesthetic-Like Mechanism:** The inhibitory effect is mediated via the conserved local anesthetic binding site, leading to a reduction in sodium currents and stabilization of the inactivated state.
- **Receptor-Independent Analgesia:** This peripheral mechanism suppresses action potential generation independently of cannabinoid receptors, identifying a novel pathway for cannabinoid-based pain relief.

References

1. Maatuf Y, Y. Kushnir, A. Nemirovski, M. Ghantous, A. Iskimov, A.M. Binshtok, & A. Priel, The analgesic paracetamol metabolite AM404 acts peripherally to directly inhibit sodium channels, Proc. Natl. Acad. Sci. U.S.A. (2025).
2. Maatuf Y, Iskimov A, Binshtok A, Priel A. The psychoactive cannabinoid THC inhibits peripheral nociceptors by targeting NaV1.7 and NaV1.8 nociceptive sodium channels. Neuropsychopharmacology (2026).