

The Mechanisms of Chronic Pain in Alzheimer's Disease

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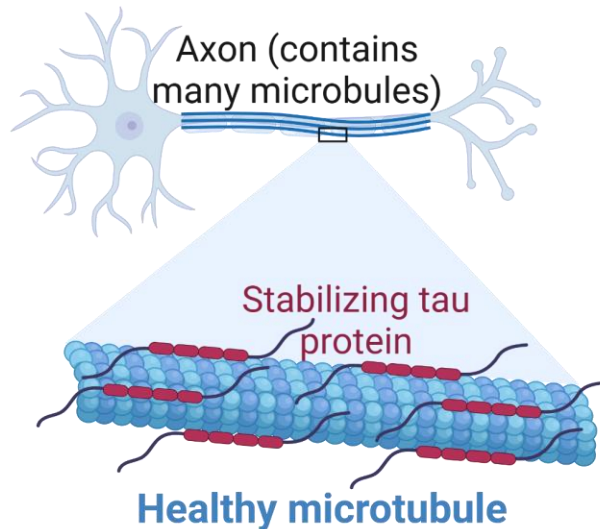
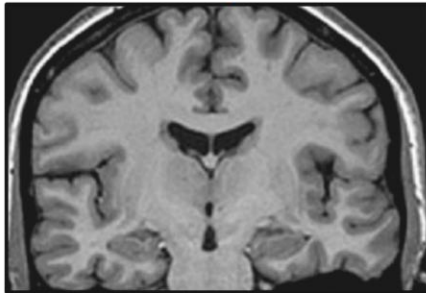
Chinese Institute for Brain Research (CIBR)

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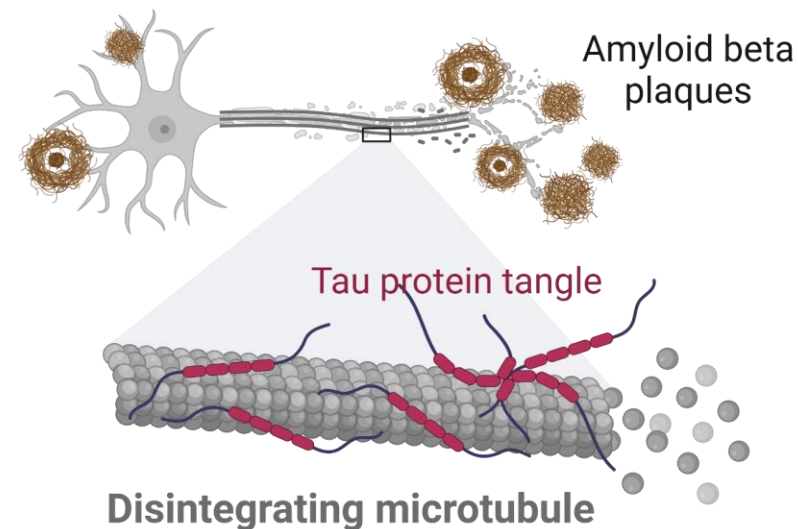
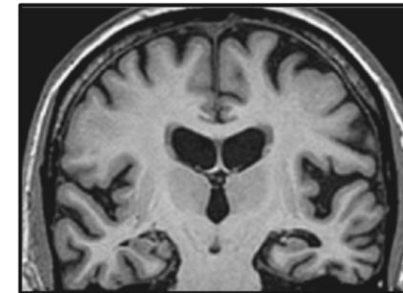
Pathology of Alzheimer's disease (AD)

- AD is characterized by progressive cognitive decline and pathologically by amyloid β ($A\beta$) plaques and Tau neurofibrillary tangles (NFTs).

Healthy brain



Alzheimer's brain



Clinical symptoms of Alzheimer's disease (AD)



Cognitive Impairment



- Memory Impairment
- Decline in Executive Function
- Visuospatial Skills Impairment
- Language Dysfunction
- Decreased Attention and Concentration

Neuropsychiatric Symptoms (Behavior and Psychology)



- Personality and Mood Changes
- Perceptual Disturbances
- Thought Content Disturbances
- Behavioral Abnormalities

Neurological Symptoms (Motor and Sensory)



Motor function

- Unsteady gait, slow movement, muscle rigidity, tremor

Sensory function

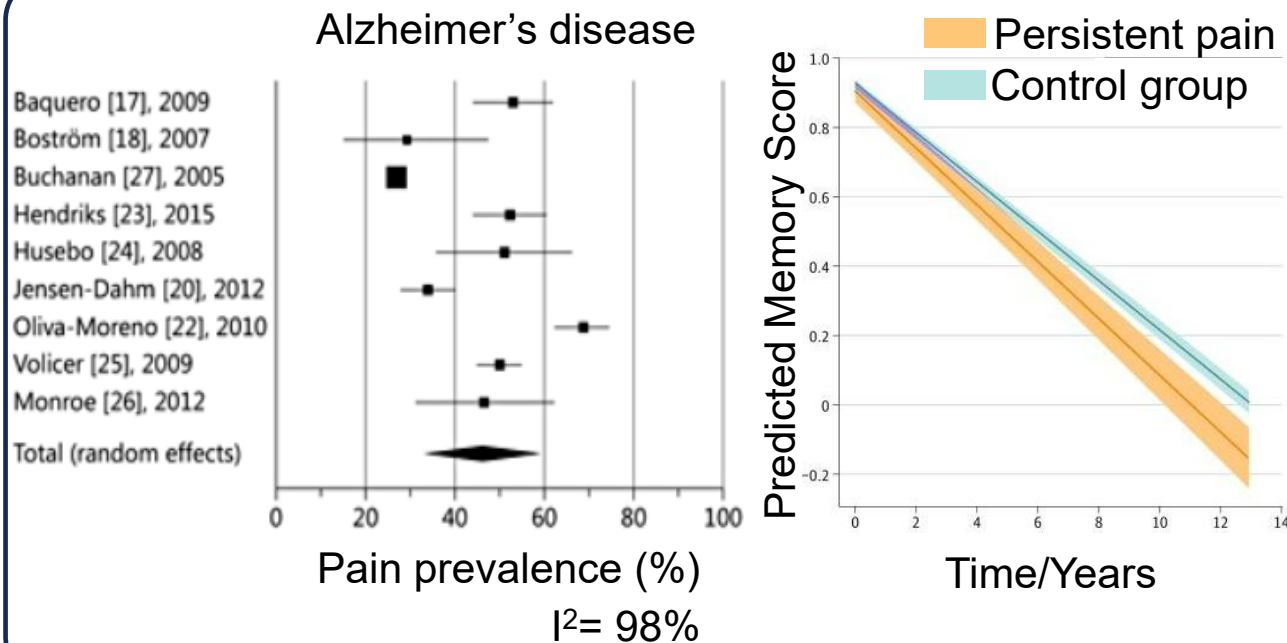
- Anosmia, Pain

Pain is prevalent among patients with moderate to severe AD



- ❑ 50%–80% of AD patients experience pain, <30% receive treatment.
- ❑ Cognitive decline in AD is positively correlated with decreased pain threshold.
- ❑ A more systematic pain assessment system has been developed for AD patients.

Prevalence of Pain in AD



Dement Geriatr Cogn Disord. 2016.
JAMA Intern Med. 2017.

Pain Assessment Scales for AD Patients

- Pain assessment in advanced dementia scale (PAINAD)
- Mobilization–observation–behavior–intensity–dementia Scale (MOBID-2)
 - Breathing • Negative vocalization • Facial expression
 - Body language • Consolability



Pain noises:
Ouch!
Groaning
Gasping
Screaming



Facial expression:
Grimacing
Frowning
Tightening mouth
Closing eyes



Defence:
Freezing
Guarding
Pushing
Crouching

Age Ageing. 2006.
J Physiother. 2017.

Anatomy basics of AD associated chronic pain

Skin

- Pathological deposition (A β , tau)
- Immune infiltration
- Nerve injury



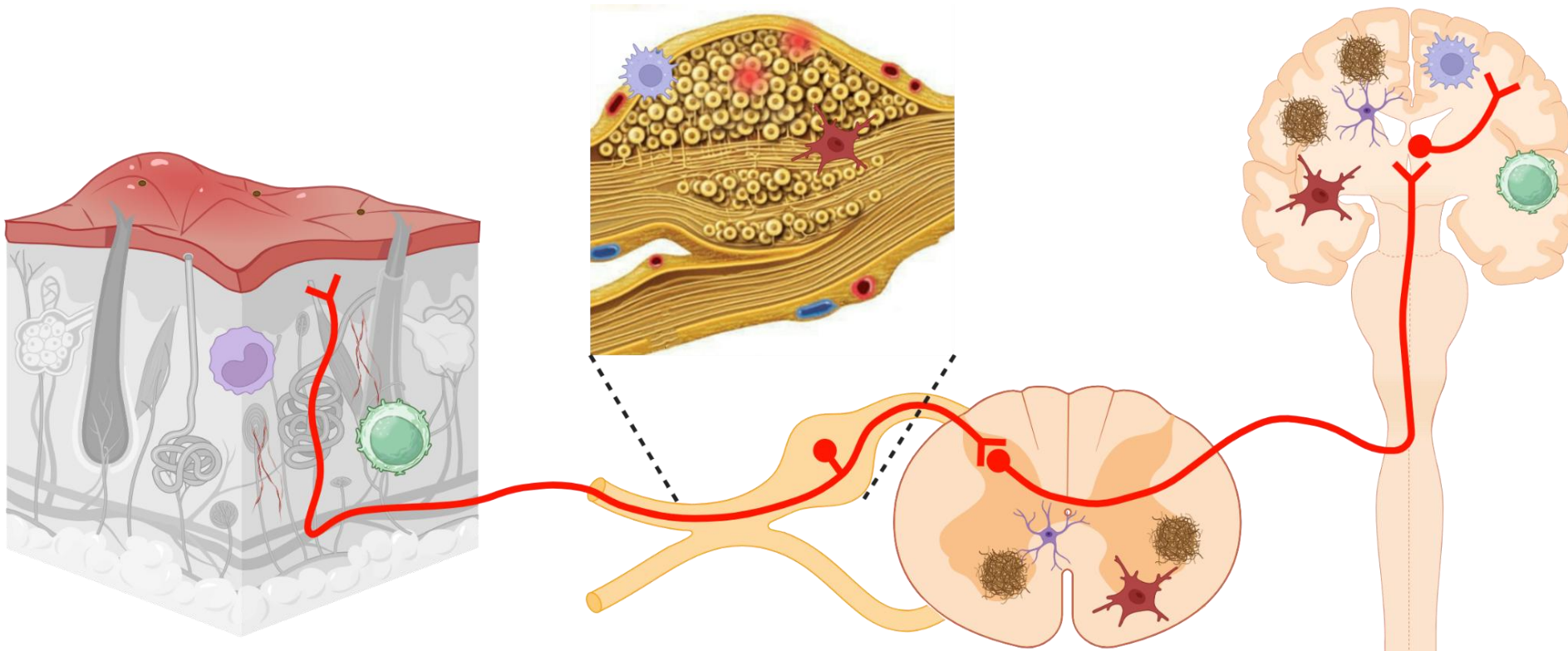
Dorsal Root Ganglion (DRG)

- Pathological deposition (A β , tau)
- Neuroinflammation
- Neuropathy



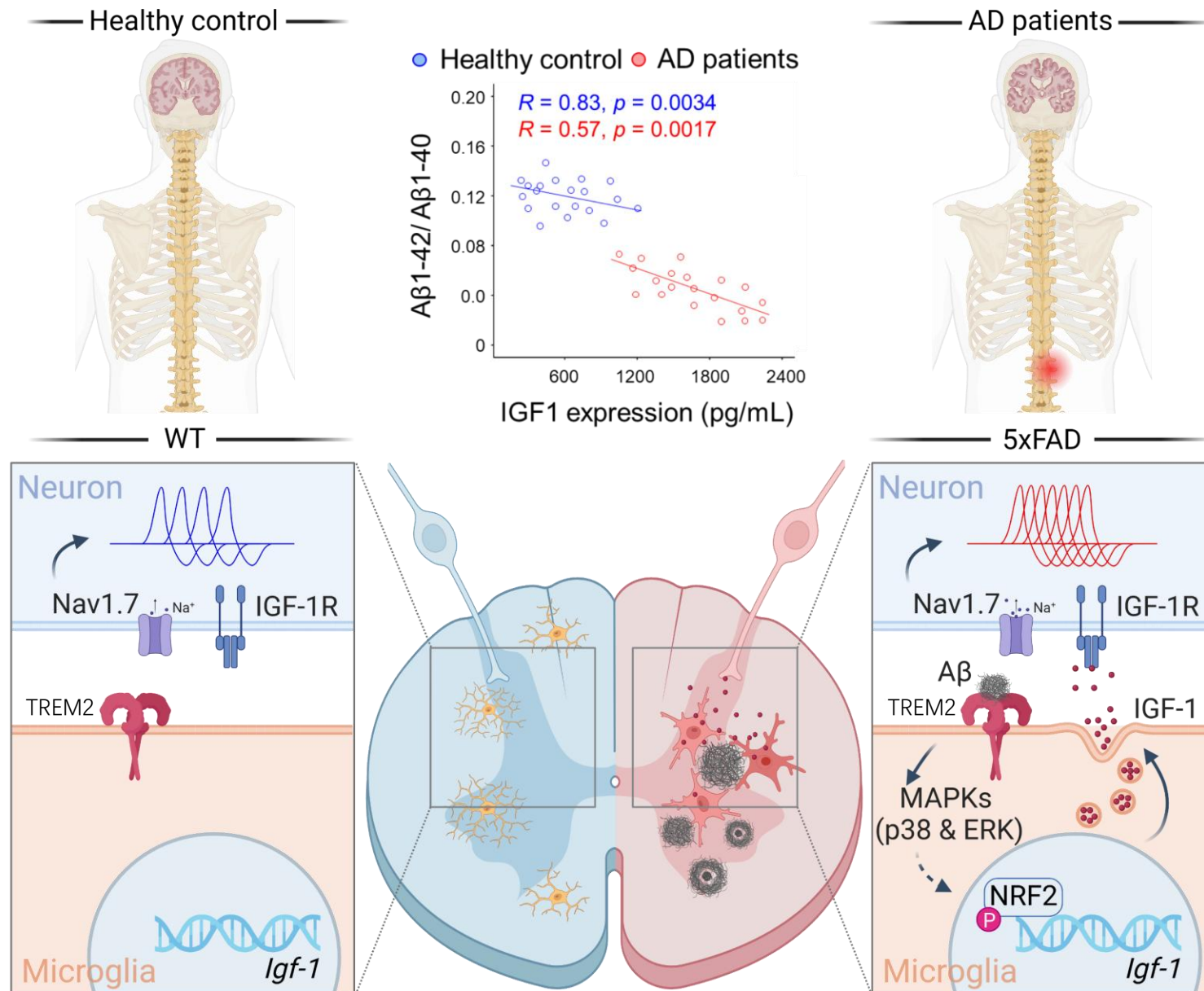
Spinal Cord and Brain

- Pathological deposition (A β , tau)
- Local immune activation
- Neuronal injury



- At the spinal cord, how does amyloid- β pathology in Alzheimer's disease activate immune cells to modulate neuronal excitability and drive chronic pain?

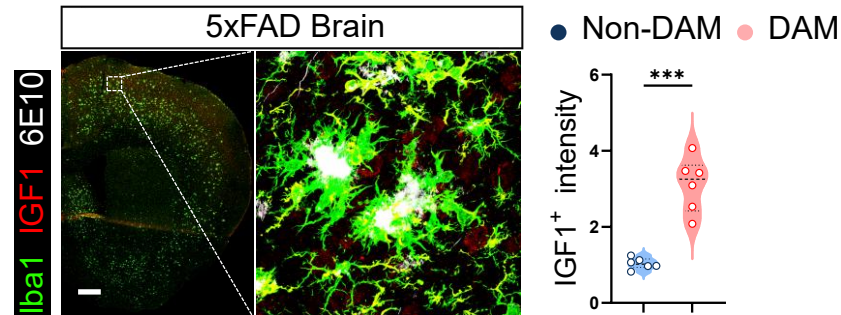
IGF-1 derived from disease-associated microglia enhanced synaptic transmission and mediate chronic pain through IGF-1R in AD patients and mouse



Preliminary work and research plan

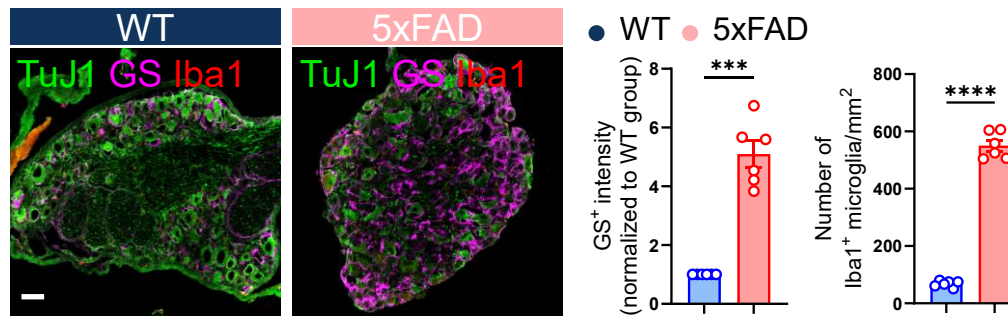


- Increased DAM IGF-1 in the brain



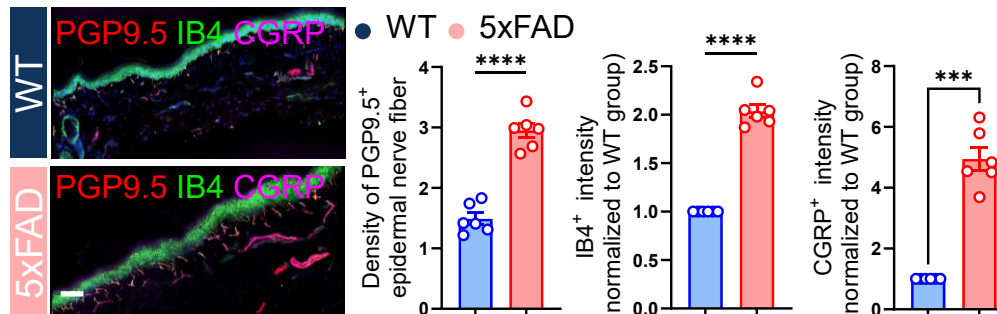
What's the role of DAM IGF-1?

- Satellite glia activation & macrophage infiltration in the DRG



How does A β activated satellite glia cells and modulate pain?

- Enhanced nociceptive innervation in the skin

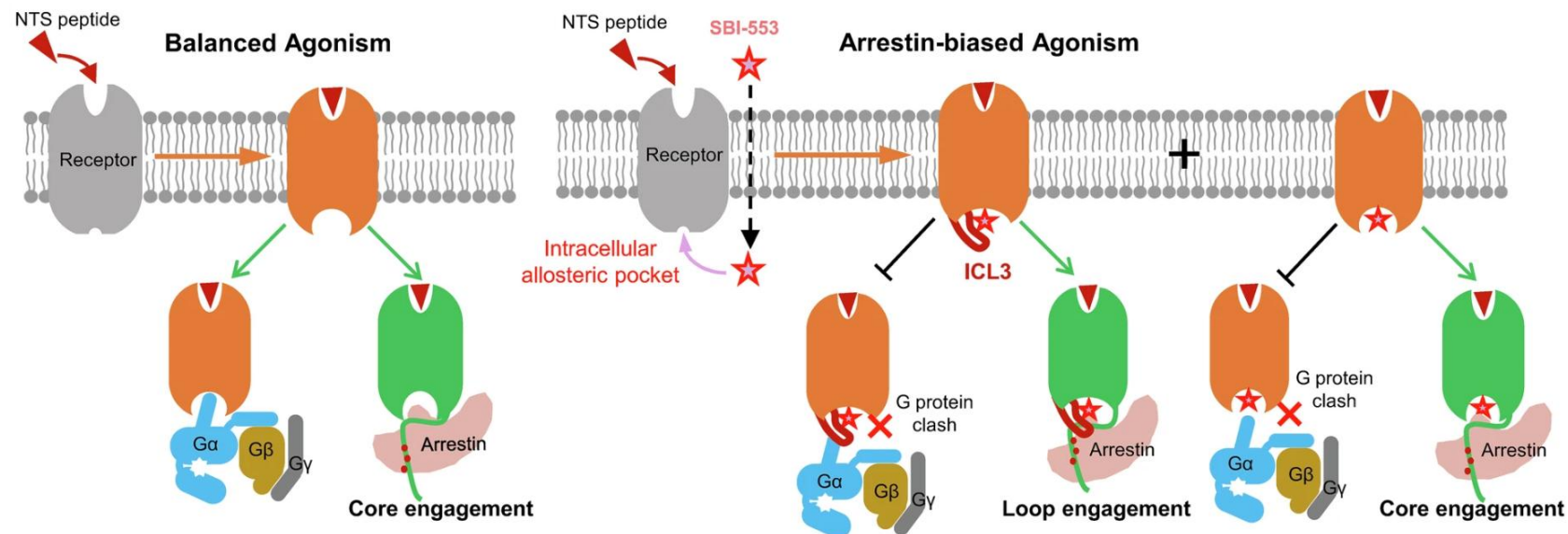


How does AD pathology affect nerve infiltration of the skin?

Background — NTSR1, β -arrestin-2 and Pain Modulation

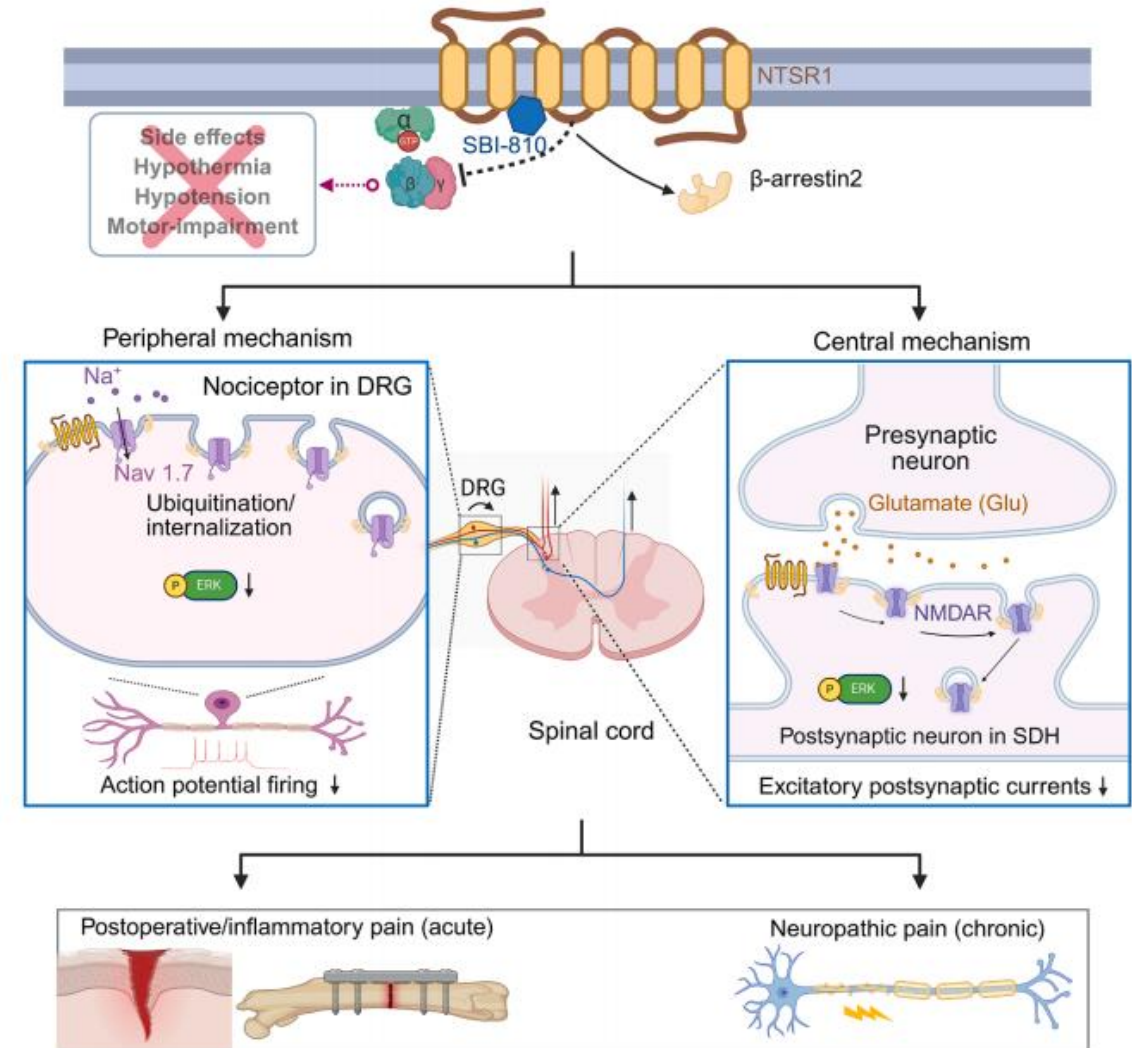


- NTSR1 (Neurotensin Receptor 1) is a GPCR in the CNS involved in pain, mood, and cognition. Conventional agonists co-activate Gq and β -arrestin pathways, leading to side effects such as hypotension and hypothermia.
- SBI-553 or SBI-810 binds an intracellular allosteric pocket, remodeling the ICL3–TM6 region into a “loop engagement” conformation, enabling β -arrestin coupling while excluding G-protein binding.
- The remodeled ICL3 and TM6 sterically clash with G α 's α N-helix, preventing G-protein/GRK assembly and leaving only β -arrestin signaling active. β -arrestin-biased activation of NTSR1 enables non-opioid, low-side-effect analgesia and neuromodulation.



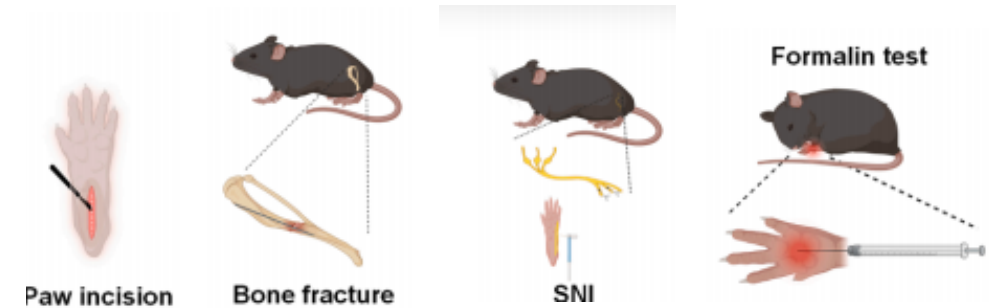
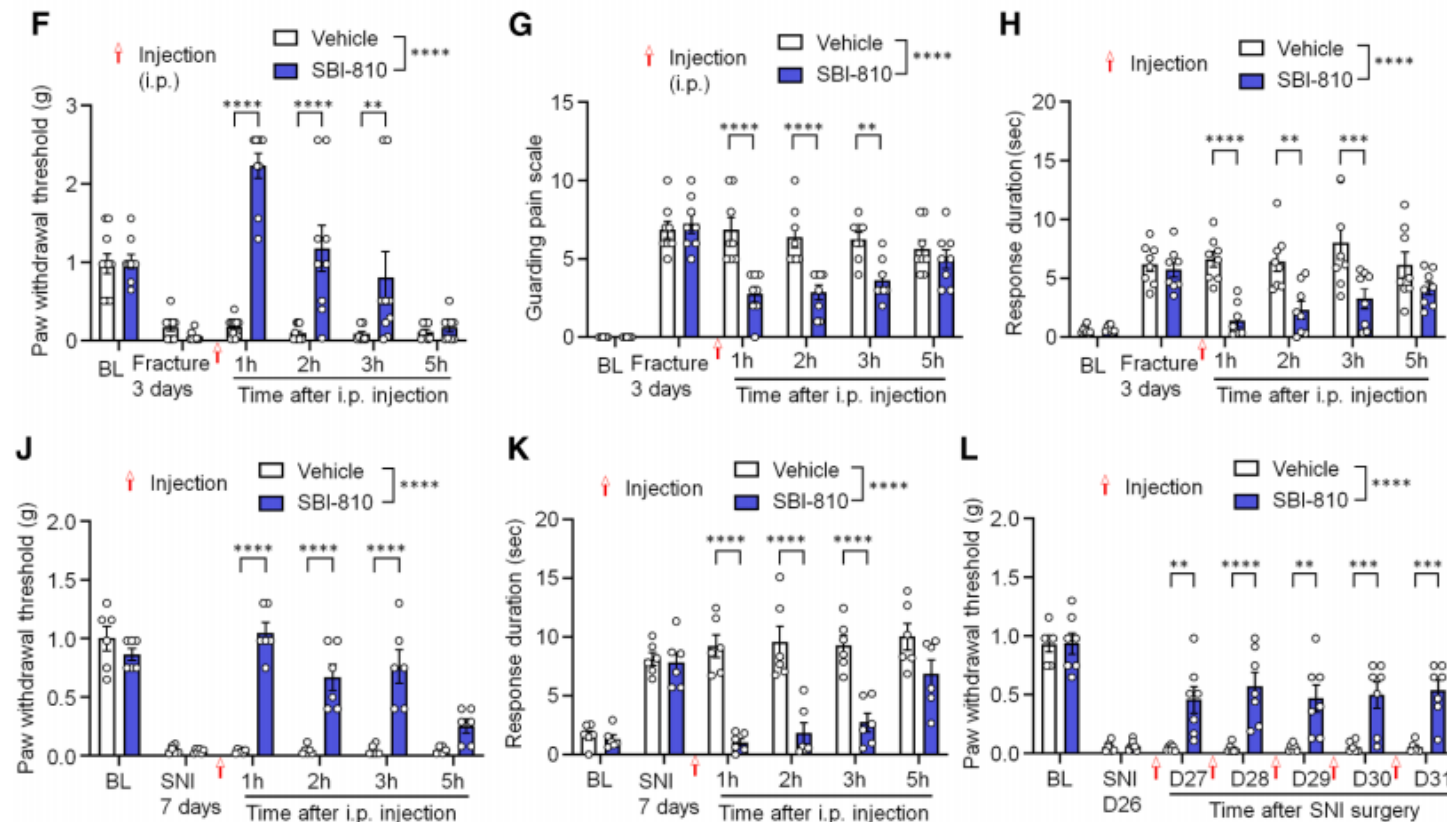
Proposed Mechanistic Model

- ❑ **Peripheral Effect:** NTSR1- β arr2 reduces Nav1.7 surface expression, decreasing neuronal excitability and suppressing peripheral pain.
- ❑ **Central Effect:** NTSR1- β arr2 signaling suppresses NMDA receptors and ERK, reducing pain transmission in the spinal cord.
- ❑ **Dual Effect:** NTSR1- β arr2 suppresses both peripheral and central sensitization, providing analgesia.
- ❑ **Analgesic Effect:** SBI-810 provides analgesia via NTSR1- β arr2, avoiding opioid side effects.



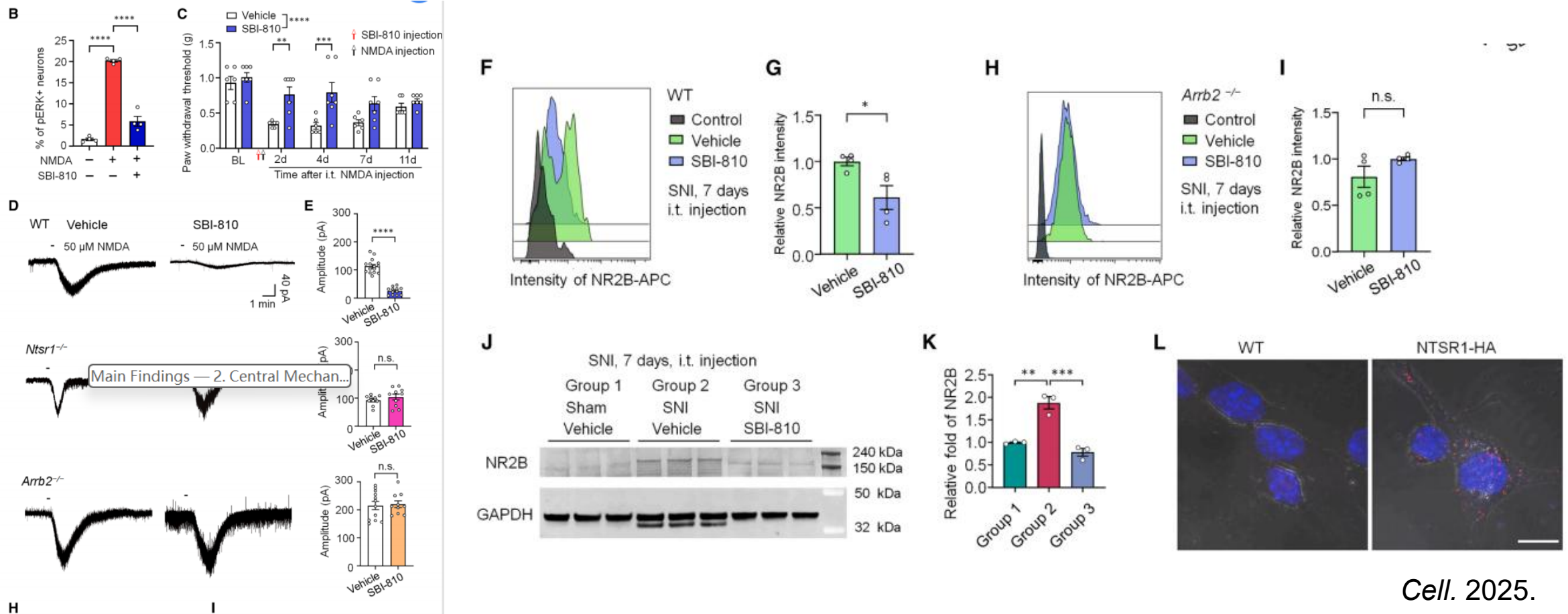
Main Findings — Analgesic Efficacy and Safety

- Systemic (i.p.) or intrathecal (i.t.) SBI-810 raised pain thresholds in naïve mice; effects were lost in *Ntsr1*^{-/-} and *Arrb2*^{-/-} but preserved in *Ntsr2*^{-/-} and *Arrb1*^{-/-} mice.
- Effective across pain models: post-incision, bone fracture, neuropathic (SNI, STZ), and inflammatory (CFA, formalin).



Main Findings — Central Mechanism (spinal SDH)

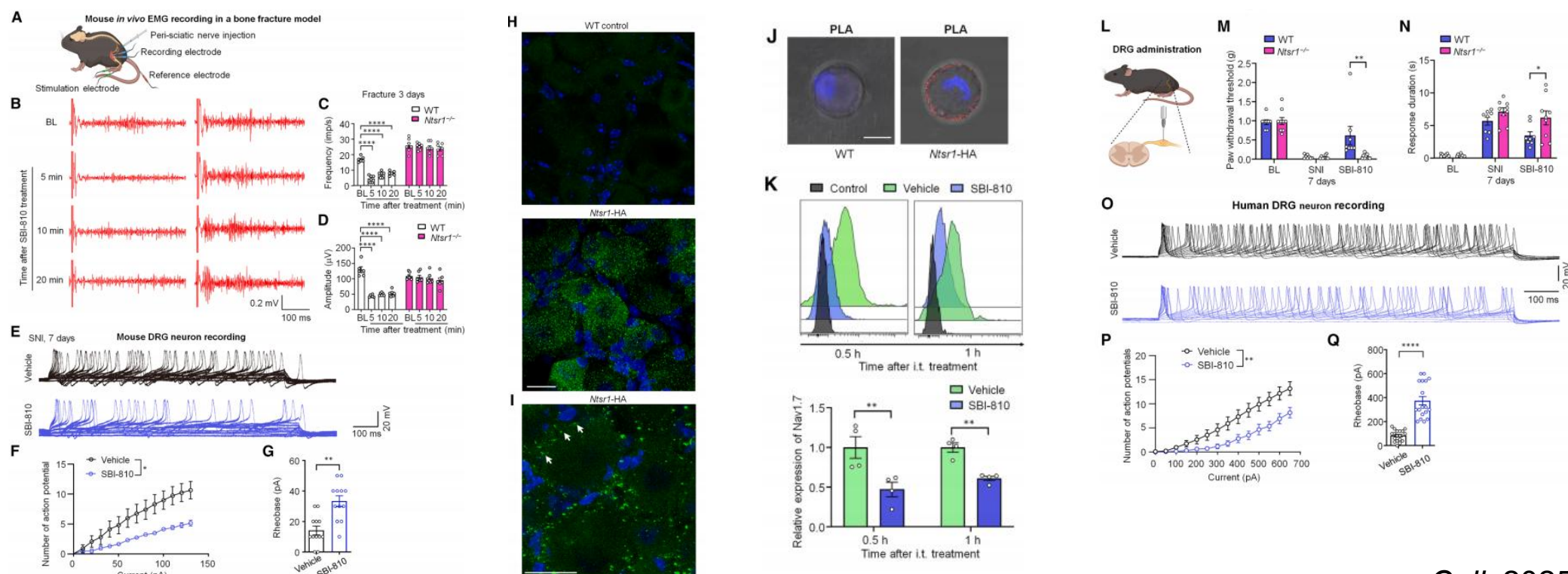
- NTSR1 → β arr2 signaling in excitatory SDH neurons reduces sEPSC frequency/amplitude.
- Blocks NMDA-induced pERK activation and currents; these effects require NTSR1 and β arr2.
- Down-regulates surface NR2B (GluN2B) but not AMPAR subunits, and reduces NMDA-driven allodynia. Proximity-ligation assays show NTSR1–NR2B colocalization.



Main Findings — Peripheral Mechanism (DRG nociceptors)



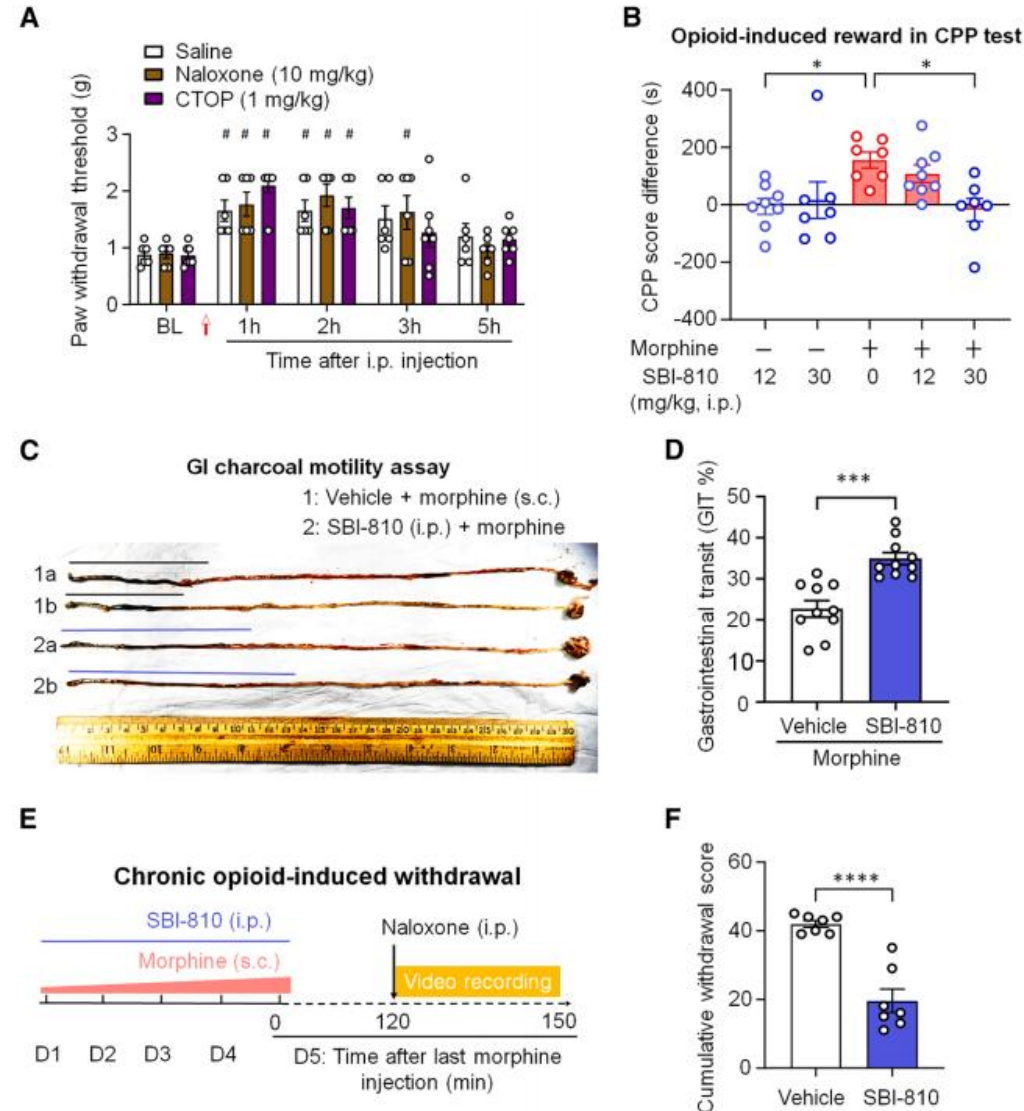
- Local or DRG delivery of SBI-810 rapidly inhibits C-fiber reflexes and reduces neuronal excitability.
- In DRG neurons (rodent and human): SBI-810 lowers AP firing, raises rheobase, and reduces surface Nav1.7 via β arr2-dependent ubiquitination and internalization.
- Endosomal inhibitors (Dy4, PS2) and ubiquitin blockers (MG132) abolish its analgesic effect, confirming a NTSR1- β arr2-Nav1.7-ERK axis.



Main Findings — Opioid Interactions



- SBI-810 does not produce CPP (reward), blocks morphine-induced CPP, and reduces constipation and withdrawal symptoms.
- It enhances acute morphine analgesia and delays tolerance and opioid-induced hyperalgesia.





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