D-cycloserine, a glycine agonist of NMDA receptor, acts as an analgesic in neuropathic rats

M. Millecamps[1], R. I. Jabakhanji[1], S. Lavarello[1], D. R. Chialvo[1], A.V. Apkarian[1]
[1]Department of Physiology, Northwestern University Medical School, Chicago, IL, 60611.

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INTRODUCTION

Human brain imaging studies in our lab indicate that cortical and sub-cortical fear conditioning pathways may be fundamental to chronic neuropathic pain behavior.

In rat, D-cycloserine has been shown to selectively enhance extinction of fear-conditioning.

We hypothesize that decreased fear-conditioning would lead to analgesic behavior in chronic neuropathic rats.

METHODS

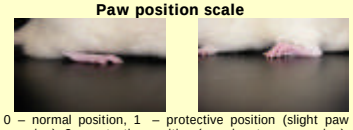
We used spared nerve injury (SNI) neuropathic rats and followed their mechanical (Von Frey filaments test), cold (acetone test) allodynia, and paw position (score from 0 to 4 an index of the intensity of the protective behavior) responses following treatment with D-cycloserine.

D-cycloserine was applied either

- **(Exp. 1)** Once orally (0, 3, 10 or 30 mg/kg),
- **(Exp. 2)** once intrathecally (0, 10 or 50 microg/rat), or
- **(Exp. 3)** for 2 weeks orally (twice daily; saline, 3, 10 or 30 mg/kg). After 3 weeks of stopping treatment, rats received a second 2-week oral treatment.
- **(Exp. 4)** Orally until the allodynia plateaus (twice daily, saline or 30 mg/kg). Response timecourse followed during and after treatment.

Eight rats / dose and group

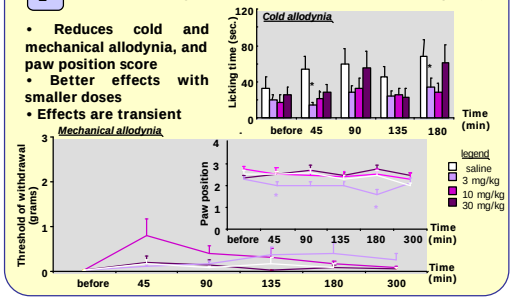
Paw position scale



0 – normal position, 1 – protective position (slight paw aversion), 2 – protective position (prominent paw aversion), 3 – heel on the floor (partial paw withdrawal), 4 – no contact (total paw withdrawal)

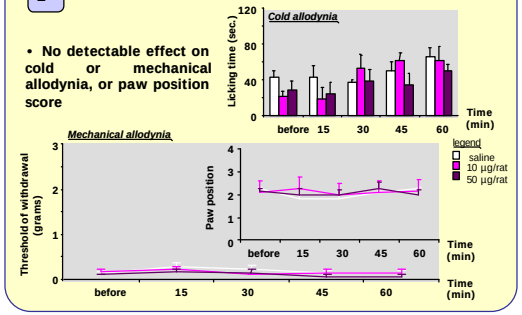
1 Acute oral D-cycloserine induces minimal analgesia

- Reduces cold and mechanical allodynia, and paw position score
- Better effects with smaller doses
- Effects are transient



2 Acute intrathecal D-cycloserine has no effect

- No detectable effect on cold or mechanical allodynia, or paw position score



CONCLUSIONS

- **Analgesic effects of D-cycloserine are probably mediated through supra-spinal mechanisms.**
- **Chronic use is more potent than acute treatment and induces chronic relieve in pain behavior.**
- **D-cycloserine probably induces neuroplastic changes in pain-fear associated pathways.**
- **Partial glycine agonists have the potential of becoming clinically significant analgesics.**

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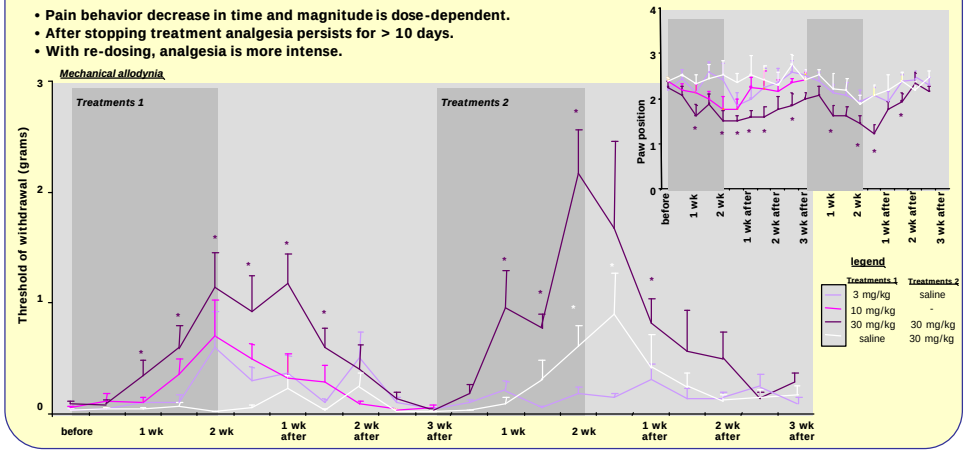
RESULTS

3 Repeated (chronic) oral D-cycloserine for 2 weeks results in robust analgesia

- Pain behavior decrease in time and magnitude is dose-dependent.
- After stopping treatment analgesia persists for > 10 days.
- With re-dosing, analgesia is more intense.



4 Repeated oral D-cycloserine for 5 weeks induces longer-lasting analgesia

- Analgesia is specific to injured paw
- After 3 weeks analgesia plateaus.
- After stopping 5-week treatment analgesia is sustained for > 4 weeks