Sarcosine, a glycine reuptake inhibitor, acts as an analgesic in an animal model for neuropathic pain

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INTRODUCTION

We recently showed that repeated oral D-cycloserine (partial agonist for glycine receptor) can decrease neuropathic behavior by potentiating NMDA transmission in the medial prefrontal cortex (mPFC) (Millecamps, et al. 2006). Here we test whether sarcosine, a glycine T1 reuptake inhibitor, has analgesic/anti-neuropathic effects. The hypothesis is that sarcosine should be analgesic in the spinal cord and anti-neuropathic in mPFC. Acute and long-term treatment effects were studied.

METHODS

We used spared nerve injury (SNI) model to assess effects of sarcosine in adult, male, Sprague Dawley rats. Tactile thresholds were assessed using Von Frey filaments. Cold allodynia (acetone test) and motor abilities (open field) were also tested. All measures were done blinded.

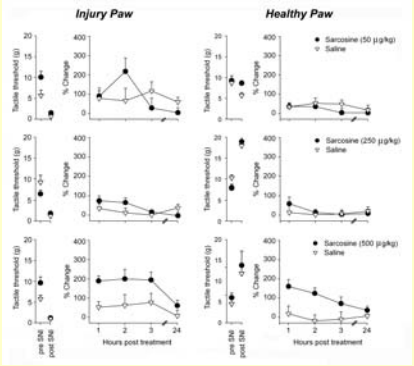
Treatments:

- Acute oral doses (Sarcosine or Saline; 50, 250 and 500 μg/kg, 2 ml/kg)
- Acute intrathecal injections (Sarcosine or Saline; 50μg, 10μl/site)
- Acute brain infusions in mPFC (Sarcosine or Saline; 50μg, 0.5μl/site)
- Chronic oral doses: rats were treated twice a day orally for 14 consecutive days (Sarcosine or Saline; 250μg/kg, 2 ml/kg). Response time course was followed during treatment and 14 days after cessation of treatment.

For brain infusions rats were anesthetized and implanted with one guide cannula (26 gauge, Plastics One Inc., Canada) using coordinates for right mPFC: anteroposterior, +2.9mm from bregma; mediolateral, -1mm from midline; dorsoventral, -4.1mm from skull surface. One week after cannulation, animals underwent SNI surgery on their left paw (contralateral side)

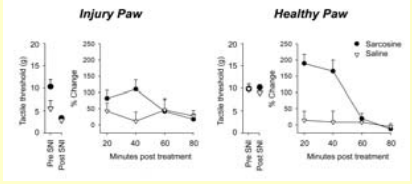
RESULTS

1 Acute Oral Treatment (gavage)



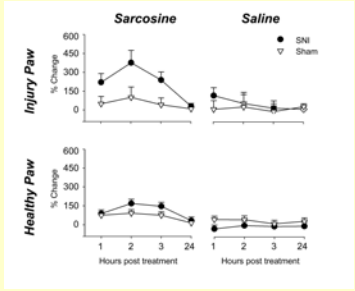
Single dose of oral reduces tactile sensitivity for the neuropathic paw and healthy paw. Each dose (50, 250 and 500 μg/kg) was contrasted to saline (n=8 rats/group). For SNI paw, there was a dose effect ($F_{2,43} = 3.7$, $p < 0.04$), and time effect ($F_{3,129} = 8.1$, $p < 10^{-4}$). For healthy paw, there was a time effect ($F_{3,141} = 3.7$, $p < 0.01$), borderline treatment effect ($F_{1,47} = 3.6$, $p < 0.06$) and significant interactions.

2 Acute intrathecal injections



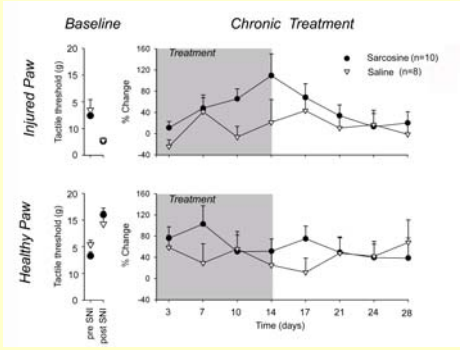
Spinal sarcosine (50μg, 10μl) vs. saline was more effective on tactile sensitivity for healthy paw. Treatment effect of healthy paw was significant ($F_{1,10} = 21.9$, $p < 0.001$), but not for injured paw.

3 Acute brain infusions (in mPFC)



Brain infusion of sarcosine mainly decreases tactile allodynia for the injured paw. SNI (n=13) and sham (n=11) rats were tested for sarcosine (50μg, 0.5μl) vs. saline. For the SNI injured paw, there were borderline main effects for type of surgery (sham vs SNI; $F_{1,19} = 3.8$, $p < 0.07$), treatment (drug vs saline; $F_{1,19} = 3.8$, $p < 0.07$), and time ($F_{3,57} = 4.9$, $p < 0.004$). For the health paw, we only see treatment and time effects.

4 Repeated (2 – week) oral treatment



Repeated treatment effects were only observed for the injured paw and only at days 10 and 14 from start of treatment. SNI rats were treated twice a day orally for 14 days. Pain behavior was tested twice a week for 28 days. Pain testing was done 15 hours after last sarcosine, to minimize contribution of acute sarcosine effects. For the SNI injured paw for first 14 days, there was a borderline main effect of treatment ($F_{1,17} = 3.6$, $p < 0.06$), as well as a time effect ($F_{3,51} = 3.6$, $p < 0.02$). All other measures were not significant.

CONCLUSIONS

The results indicate that acute sarcosine decreases tactile sensitivity for SNI injured and healthy paws. Indicating that it has both an anti-neuropathic and analgesic effects.

The analgesic effect seems to be preferentially mediated through its action in the spinal cord.

The anti-neuropathic effect seems to be preferentially mediated through the cortex (mPFC).

As long-term treatment effects only show anti-neuropathic effects, they most likely are mediated through cortical action of sarcosine.

Given the dual site of action of sarcosine, in the spinal cord probably enhancing glycinergic inhibition and in the cortex probably enhancing NMDA transmission, it should be considered a potential drug for treating human chronic pain.

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