



Neuropathic Pain Modulates Hippocampus Mediated Emotional Behavior

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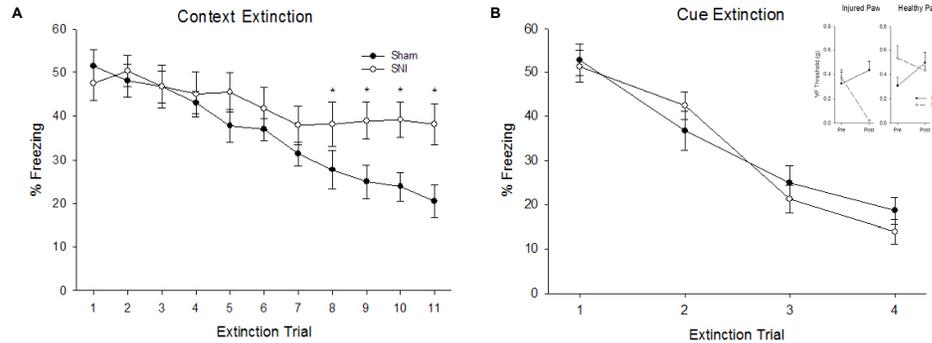
INTRODUCTION

- Chronic neuropathic pain in humans causes gross reorganization of the brain, leading to cognitive and emotional disturbances (Baliki et al., 2008).
- Among others, heightened anxiety, attentional and memory deficits accompany chronic pain (Kodama et al., 2007). The hippocampus is one of the key brain areas linking cognitive and emotional information into long-term memory.
- Context fear extinction, but not cue, is seen to be hippocampus-dependent.
- MAPK/Erk-CREB signaling cascade in the hippocampus is necessary for memory formation, and may modulate emotional responses. An increase in pErk is necessary for fear extinction.
- This study aims to determine how chronic neuropathic pain affects hippocampus-dependent behavior as well as determine underlying molecular properties accompanying these behaviors.

METHODS

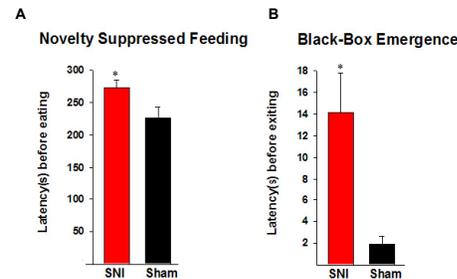
- 42 C57/B6 9-week old male mice underwent either a Sham or Spared-Nerve Injury surgery on the left hind paw (Sham=20, SNI=22). 21 mice underwent the same on the right hind paw (Sham=10, SNI=11).
- SNI animals included in the analysis had a significant decrease in withdrawal threshold on the injured paw (Von Frey thresholds). Sham animals showed no change.
- Subgroup of 21 mice (left paw) underwent context and cue fear extinction and conditioning. Brains of these mice were taken for immunohistochemistries for dpErk, cFos, and pCreb.
- Subgroup of 42 mice (21 left paw, 21 right paw) were observed for anxiety-like behaviors on the Novelty Suppressed Feeding, Black-box Emergence, and Elevated Plus Maze tasks.
- Of the anxiety tested mice, 20 brains were taken for immunohistochemistries (10 SNI) and 22 for Western blots (12 SNI), where deltaFosB and dpErk were investigated.

1 Impaired Extinction to Context, but not to Cue, in SNI Mice



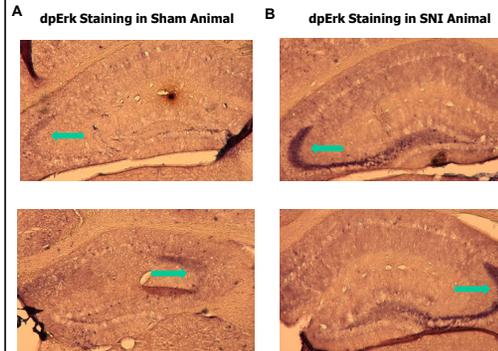
- A.** Context fear extinction. All animals demonstrated fear conditioning on testing day 1 (SNI n=11, Sham n=10). A significant difference is seen in context extinction, $F_{19,190}=3.6$, $p<0.001$ with SNI animals showing an inability to extinguish to context. In particular, this difference is first significant on extinction day 8.
- B.** There is no difference in cue fear extinction between SNI and Sham animals ($F_{19,57}=2.02$, ns).

2 Increases in Anxiety-like Behaviors in SNI Mice



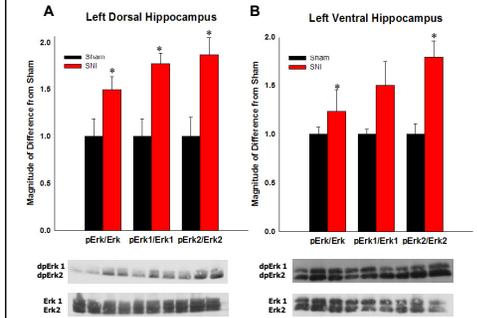
- A.** Latency to start eating was significantly different ($t_{(40)}=2.15$, $p=0.04$) between SNI and Sham groups (SNI n=22, Sham n=20), with SNI animals having a significantly longer latency to start eating the food than the Sham animals. Latency was capped at 5 minutes.
- B.** Latency to exit the dark box was significantly different between the two groups ($t_{(39)}=3.57$, $p=0.001$) with SNI animals having a longer latency than Sham animals to leave the dark box (SNI n=21, Sham n=20).
- No differences were seen between SNI and Sham animals on the elevated-plus maze task.

3 Overexpression of dpErk in Anterior Hippocampus



- A.** Anterior hippocampus of a Sham animal stained with for dpErk. Arrows pointing towards concentration of dpErk staining in CA3.
- B.** Anterior hippocampus of an SNI animal stained for dpErk. Arrows pointing to concentration of dpErk staining in CA3.

4 dpErk Upregulation in Ipsilateral Hippocampus



- A.** In the left dorsal hippocampus, SNI animals had a significantly greater ratio of dpErk:Erk than Sham animals, $t_{(9)}=3.81$, $p=0.005$. Both dpErk1 and dpErk2 ratios are significantly increased in the SNI animals in this brain region when compared to Sham animals.
- B.** SNI animals had a significantly greater ratio of dpErk:Erk in the left ventral hippocampus than Sham animals, $t_{(8)}=3.31$, $p=0.01$. In particular, dpErk2:Erk2 is significantly greater in these SNI animals than in Sham animals while dpErk1:Erk1 is not.

CONCLUSIONS

- SNI animals are impaired in contextual fear extinction, but not cue fear extinction, suggesting a hippocampus specific change.
- Upregulation of dpErk in SNI animals (non-fear conditioned) is seen only ipsilateral to injury. This laterality suggests a specific effect of chronic pain and not chronic stress.
- Upregulation of dpErk without fear extinction in SNI mice suggests an underlying change in hippocampal functioning. This upregulation may cause an inability of these mice to have a significant increase in dpErk during extinction when compared to baseline, leading to their behavioral deficit in context extinction.
- This upregulation may also be modulating emotional behavior, such as anxiety, as seen in the SNI mice.
- This is the first evidence for specific effects of chronic neuropathic pain on hippocampus mediated behavior and molecular properties.

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