Spinal Anesthesia and Tau Trafficking: Reducing Pain-Induced Tau Phosphorylation and Postoperative Delirium

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BACKGROUND

Postoperative delirium is a prevalent postoperative neurocognitive disorder, with postoperative pain identified as a key trigger [1]. Our previous study demonstrated that surgical incision in foot induced delirium-like behavior in mice [2].

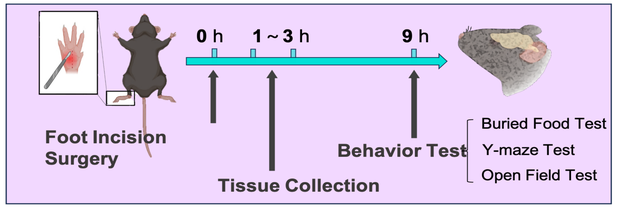
Tau hyperphosphorylation, particularly at threonine 217 (Tau-PT217), is the pathogenesis and blood biomarker of Alzheimer's disease [3]. However, the effects of spinal anesthesia on the pain-induced Tau phosphorylation remain undetermined. We hypothesize that pain induces Tau phosphorylation at spinal cord and promotes the trafficking of phosphorylated Tau from spinal cord to brain.

METHODS

We employed female C57BL/6 mice (12–16 weeks old) in this study. The incisional pain model was established as previously described [4]. Briefly, a 5-mm longitudinal incision was made through the skin and fascia of the hind paw under anesthesia to induce pain.

Mice were randomly assigned to four intervention groups.

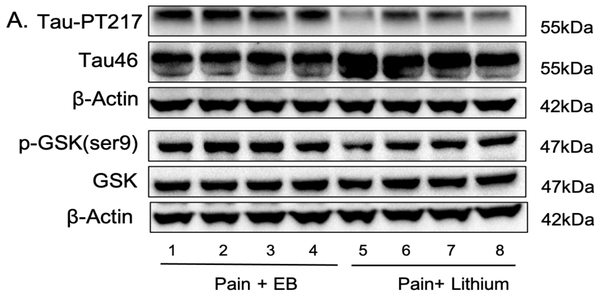
(1) Evans Blue (EB) group (control): EB dye (2 μL, 0.1%) was intrathecally injected through the spinal dura mater, penetrating the spinal cord;
(2) EB + Lithium group: EB dye was combined with lithium chloride (2 μL, 20 mM, the inhibitor of Tau phosphorylation) and injected at the same spinal location;
(3) Saline (control) group: saline was injected intrathecally into the cerebrospinal fluid (CSF) space via the L5-L6 intervertebral region;
(4) Ropivacaine group: ropivacaine (0.75%, 5 μL) was similarly injected into the CSF space through the same route.



RESULTS

Intrathecal administration of lithium chloride and ropivacaine significantly reduced hippocampal Tau-PT217 levels compared to their respective controls (Figures 1 & 2, $p < 0.01$ and $p < 0.05$). Interestingly, the activity of GSK3β, responsible for Tau phosphorylation, was slightly increased rather than decreased in both treatment groups. These findings imply that the Tau-PT217 in hippocampus may, at least partially, results from the trafficking of Tau-PT217 from spinal cord. Immunofluorescence analysis of the lumbar spinal cord showed a significant reduction in Tau-PT217 levels in the Lithium-treated group compared to EB controls (Figure 3, $p < 0.05$). Quantitative fluorescence intensity analysis further supported this finding.

Figure 1. Lithium chloride reduces hippocampal Tau-PT217 levels but decreases p-GSK3β levels in a pain-induced model.



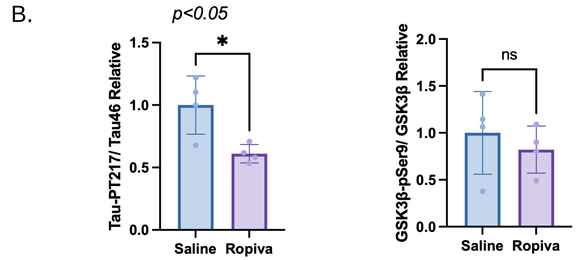


Figure 2. Ropivacaine reduces hippocampal Tau-PT217 levels without significantly altering GSK3β-pSer9 levels in a pain-induced model.

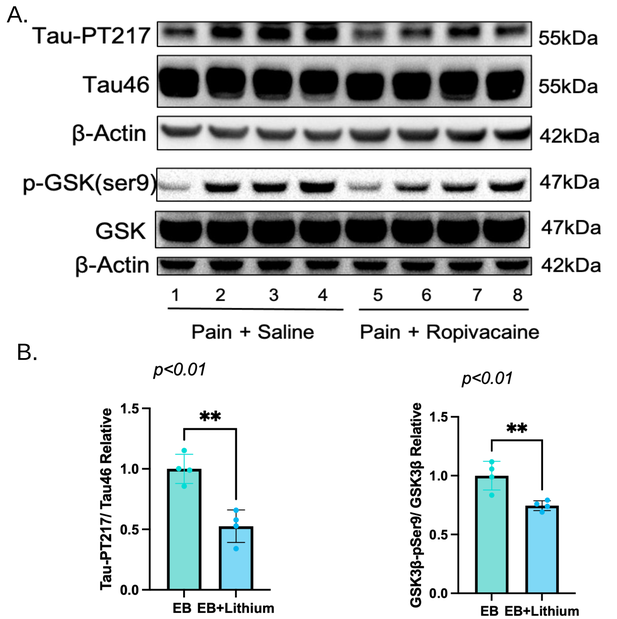
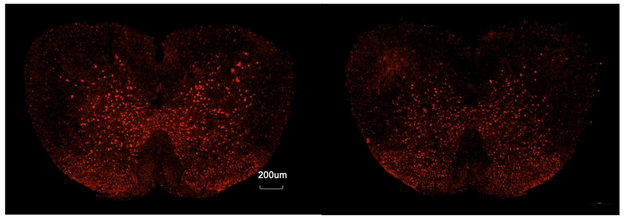


Figure 3. Intramedullary lithium administration reduces spinal Tau-PT217 levels in a pain-induced model.



Pain + EB Pain + EB + Lithium

SUMMARY/CONCLUSIONS

This study demonstrates that pain induced Tau phosphorylation in spinal cord and the locally generated Tau-PT217 can travel from spinal cord to hippocampus of mice. Intrathecal (ropivacaine) and intramedullary (lithium) interventions significantly reduce pain-induced Tau-PT217 accumulation in the hippocampus and spinal cord.

These results suggest that spinal interventions targeting tau phosphorylation may hold promise for preventing or treating postoperative delirium, pending confirmative studies..

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