Differential Dose-dependent Effects of MK801 Pretreatment on Post-TBI Mortality, NMDAR and ERK Expression, and Signal Transduction in the Developing Rat

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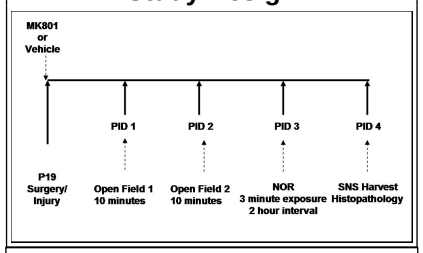
Introduction

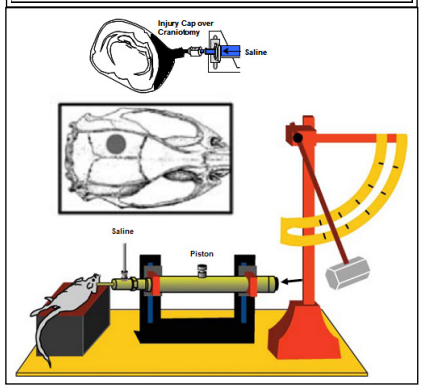
Lateral fluid percussion injury (LFP) in postnatal day 19 (P19) rats has been associated with decreased NMDAR-mediated molecular signaling and cognitive deficits during the first post-injury week. The noncompetitive NMDAR antagonist MK801 is neuroprotective in adult models of TBI. We hypothesized that pre-injury NMDAR blockade may be neuroprotective, preventing post-injury memory impairments and down-regulation of the NMDA signal-transduction pathway.

References

Krapivinsky G et.al., The NMDA receptor is coupled to the ERK pathway by a direct interaction between NR2B and RasGRF1. Neuron. 2003 Nov 13;40(4):775-84.
Atkins CM et.al., Deficits in ERK and CREB activation in the hippocampus after traumatic brain injury., Neurosci Lett. 2009 Aug 7;459(2):52-6.

Study Design

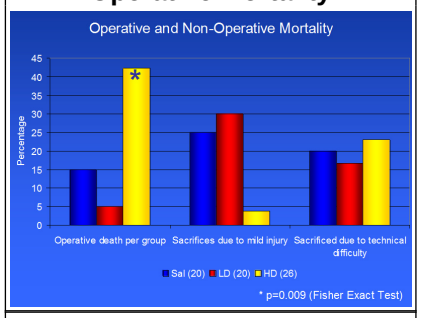




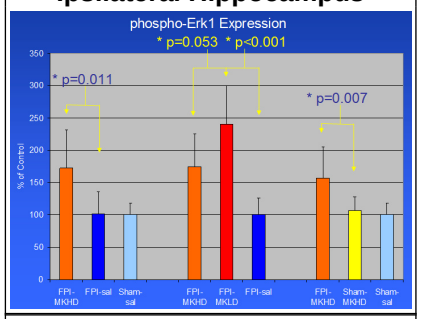
Methods

P19 Sprague-Dawley rats (n=88) underwent sham or LFP. Rats were pre-treated with intra-peritoneal (i.p.) saline, low-dose MK801 (0.1mg/kg), or high-dose MK801 (1mg/kg - neurotoxic) 20 minutes before LFP (FP-Sal, FP-LD, FP-HD respectively). Sham surgeries were performed with saline or high-dose MK801 injections (Sham-Sal and Sham-HD). Open field analyses were performed on PID 1 and 2. Novel object recognition (NOR) was performed on PID 3. Immunoblotting for NMDAR, Erk 1&2, and phospho-Erk 1&2 (pErk) was performed on PID4.

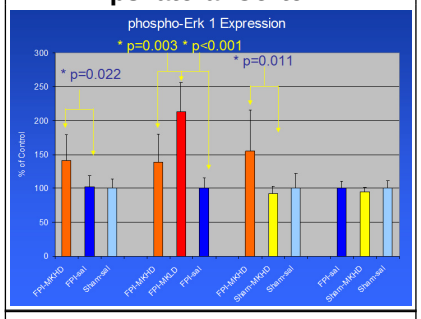
Operative Mortality



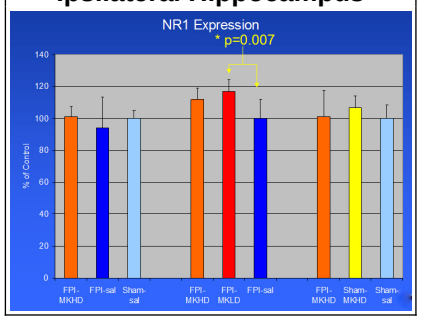
Ipsilateral Hippocampus



Ipsilateral Cortex



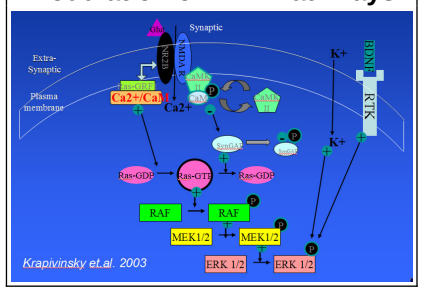
Ipsilateral Hippocampus



Results

- Mortality rates differed significantly by MK801 dose: FP-Sal 15%-(3/20), FP-LD 5%-(1/20), and FP-HD 42%-(11/26) (p=0.009).
- There was a moderate increase of NR1 and Erk1 in the FP-LD hippocampi (16.9%,p=0.007 and 26.4%,p=0.009) and NR1 in the FP-LD cortex (18.4%,p=0.043).
- Interestingly, pErk1 and pErk2 increased in the hippocampi of both the FP-LD group (140%,p=0.001 and 81%,p=0.001) and the FP-HD group (75%,p=0.026 and 38%,p=0.03).
- The higher dose of MK801 appears to have a paradoxical effect on pErk1 and pErk2
- No behavioral differences in NOR or open field rearing and exploration were seen.
- There was no evidence of gross structural damage seen on histopathology.

Modulation of ERK Pathways



Conclusions

- Post-injury mortality increased following LFP with pre-treatment of MK801 (1mg/kg), but not with low dose MK801 (0.1mg/kg).
- There was a striking increase in pErk1 and pErk2 in FP-Low Dose with less of an effect in the FP-High Dose.
- No significant differences were noted with NR2A/B expression or behavioral analyses.
- This suggests that pre-injury NMDA antagonism with high-dose MK801 may be neurotoxic with increased mortality and less upregulation of downstream pERK activation, but that low-doses may confer some benefit on these molecular pathways.