Effects of Intravenous Ketamine Infusion on Neuroinflammation Following Mild Traumatic Brain Injury in Sprague-Dawley Rats

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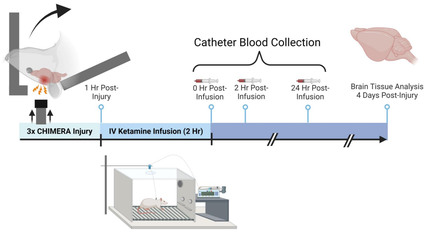
BACKGROUND

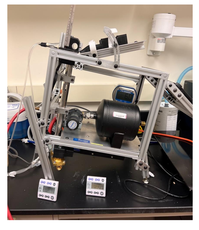
- Mild traumatic brain injury (mTBI), which affects millions of people around the world annually, may cause white matter damage, neuroinflammation, and neuropsychological deficits.
- One of the main targets for treatment of mTBI is the secondary injury process, which involves inflammatory cascades occurring after the primary brain injury.
- Ketamine, a multi-modal trauma analgesic with potential neuroprotective and immunomodulatory properties,[1,2] is widely used in the context of traumatic injury. However, its effects on the secondary injury following mTBI are not well understood.
- The goal of the study was to characterize the CHIMERA as a rodent mild TBI model and to assess subanesthetic doses of intravenous (IV) ketamine as a potential treatment option for mTBI.

METHODS

Study Design and Timeline of Sample Collection



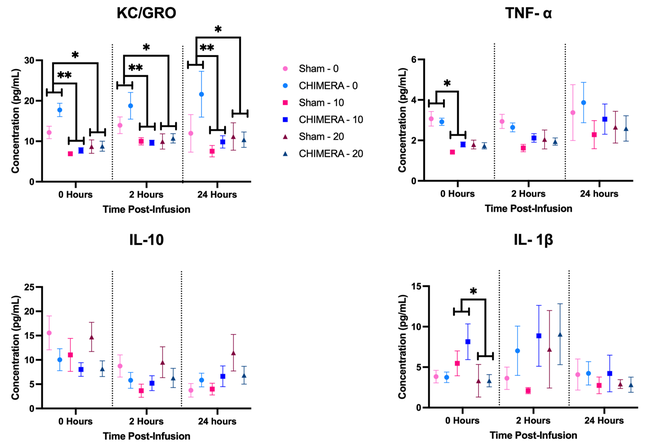
CHIMERA



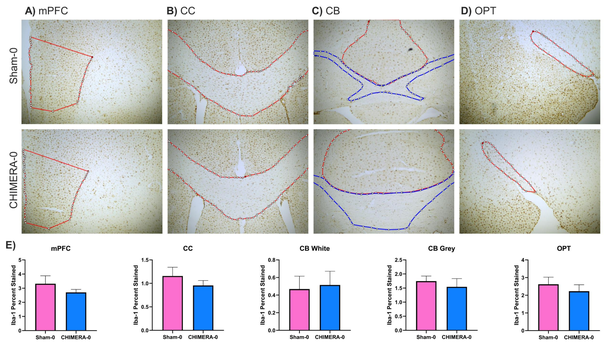
- The Closed-Head Impact Model of Engineered Rotational Acceleration (CHIMERA) is a recent technique that replicates the biomechanics of an impact TBI in humans.
- Adult male Sprague-Dawley rats with indwelling jugular venous catheters were randomized to six groups using a factorial design (CHIMERA x ketamine).
- Animals received either sham or CHIMERA injury under isoflurane anesthesia (1.5 J, 5-10 seconds between 3 impacts).[1]
- One hour after the CHIMERA injury, animals received a single IV ketamine infusion (0, 10, or 20 mg/kg, 2 hour-period).
- Catheter blood samples were collected at multiple time points for measurement of plasma cytokines including KC/GRO, TNF-α, IL-10, and IL-1β using the MSD Multiplex Immunoassay.[2]
- Brain tissue samples were collected at post-injury day 4 (PID-4) for analysis of microglia (Iba-1), astrocytes (GFAP), and axonal injury (silver staining) in multiple brain regions including the medial prefrontal cortex (mPFC), corpus callosum (CC), cerebellum (CB), and optic tract (OPT).

RESULTS

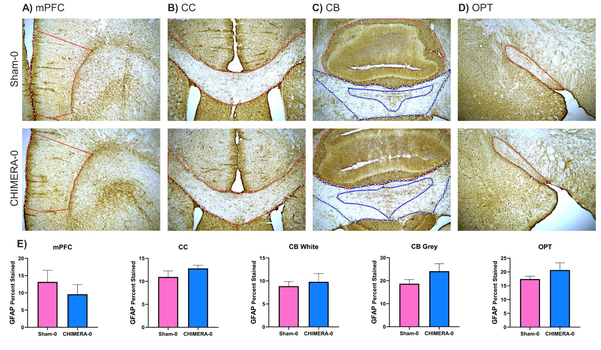
Immunomodulatory Effects of Ketamine on Plasma Cytokines



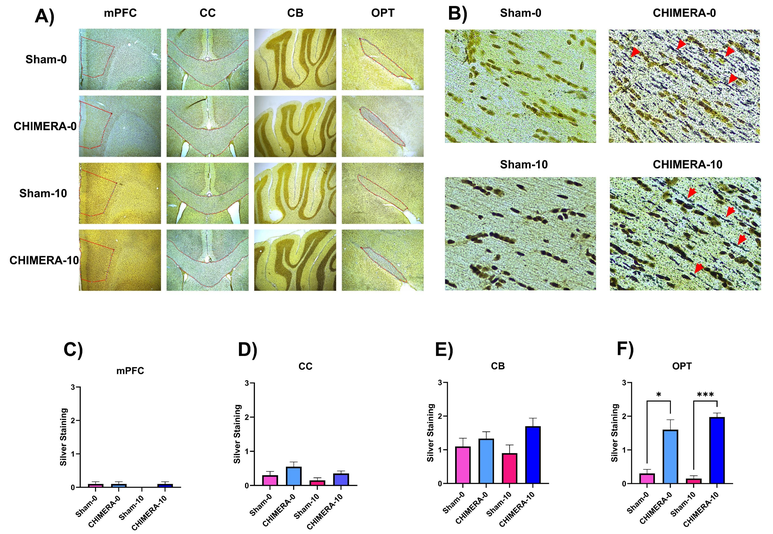
No Effects of CHIMERA on Microglial Activation at PID-4



No Effects of CHIMERA on Astrocytic Activation at PID-4



CHIMERA Increased Axonal Injury in the Optic Tract at PID-4



CONCLUSIONS

- The single-session CHIMERA injury did not produce significant impacts on microglial or astrocytic activation in any brain regions investigated.
- However, CHIMERA injury produced significant axonal injury in the optic tract (white matter damage), consistent with previous studies.[3]
- Preliminary results indicate that this closed-head injury may produce microglial activation in the cortical injury site of animals.
- A subanesthetic IV ketamine infusion produced transient immunomodulatory effects on plasma cytokines without affecting neuroinflammation in the brain.
- Further studies are necessary to investigate the comprehensive effects of mTBI and IV ketamine on cytokines, white matter damage, and neuroinflammation.

REFERENCES

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