Potential Pathognomonic Phenotype of Axonal Pathology and Mechanisms of Primary Blast Traumatic Brain Injury

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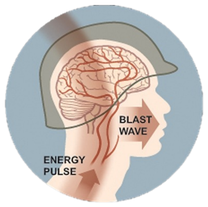
Background

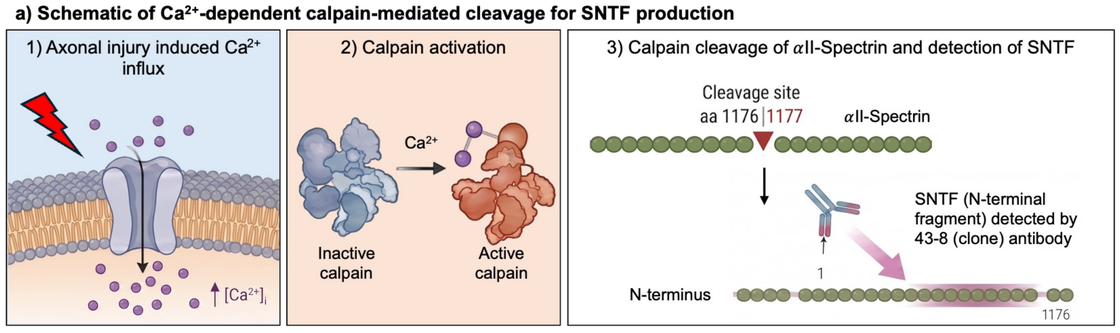
Primary blast traumatic brain injury (TBI) is highly prevalent among military personnel, yet its underlying neuropathology remains poorly defined.



Diffuse axonal injury (DAI) is a key pathologic substrate of blunt TBI. However, despite numerous examinations, the classical neuropathological hallmark of DAI, detected by amyloid precursor protein (APP)+ axonal swellings resulting from axonal transport interruption, has been largely absent or only sparsely identified in blast TBI.

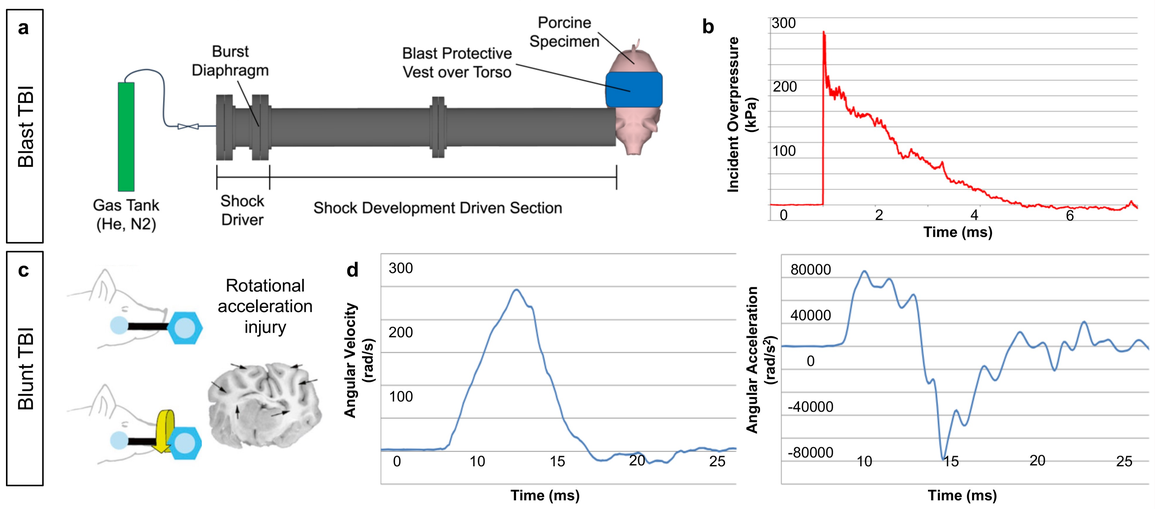
Emerging evidence supports that DAI represents multiple axonal pathology phenotypes. Notably, we have previously identified a proteolytic fragment of αII-spectrin, "**SNTF**", as a novel pathologic phenotype of axonal degeneration. However, no previous studies have examined the extent and distribution of SNTF accumulation in blast TBI and compared it to APP axonal pathology or to blunt TBI.

a) Schematic of Ca^{2+}-dependent calpain-mediated cleavage for SNTF production



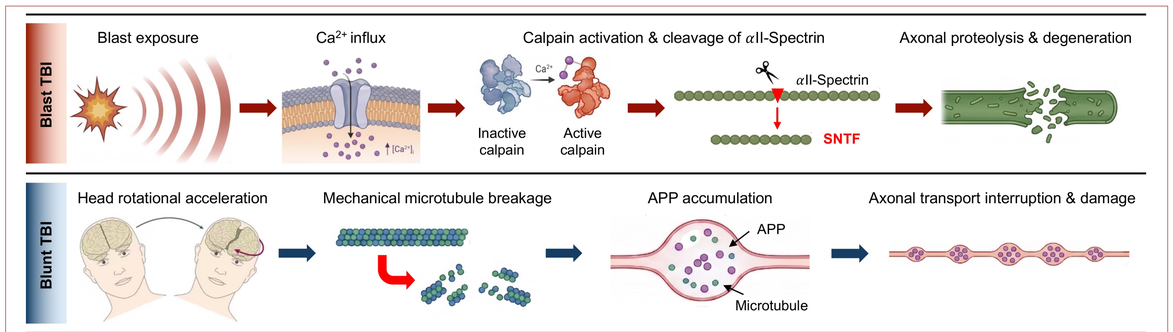
Methods

- Swine model of primary blast TBI: Female swine (n=14) were exposed to a compressed-gas shock tube generated blast wave, producing an average peak overpressure at 283.9 ± 130.9 kPa, along with a positive phase duration of 3.84 ± 1.87 ms and an impulse of 351.6 ± 205.3 kPa·ms. Sham control animals (n=3) received all procedures described above except for blast exposure.
- Swine model of rotational acceleration TBI: Female swine (n=4) were injured using a HYGE pneumatic actuator, producing an average maximum angular velocity of 234.2 ± 19.2 rad/s.



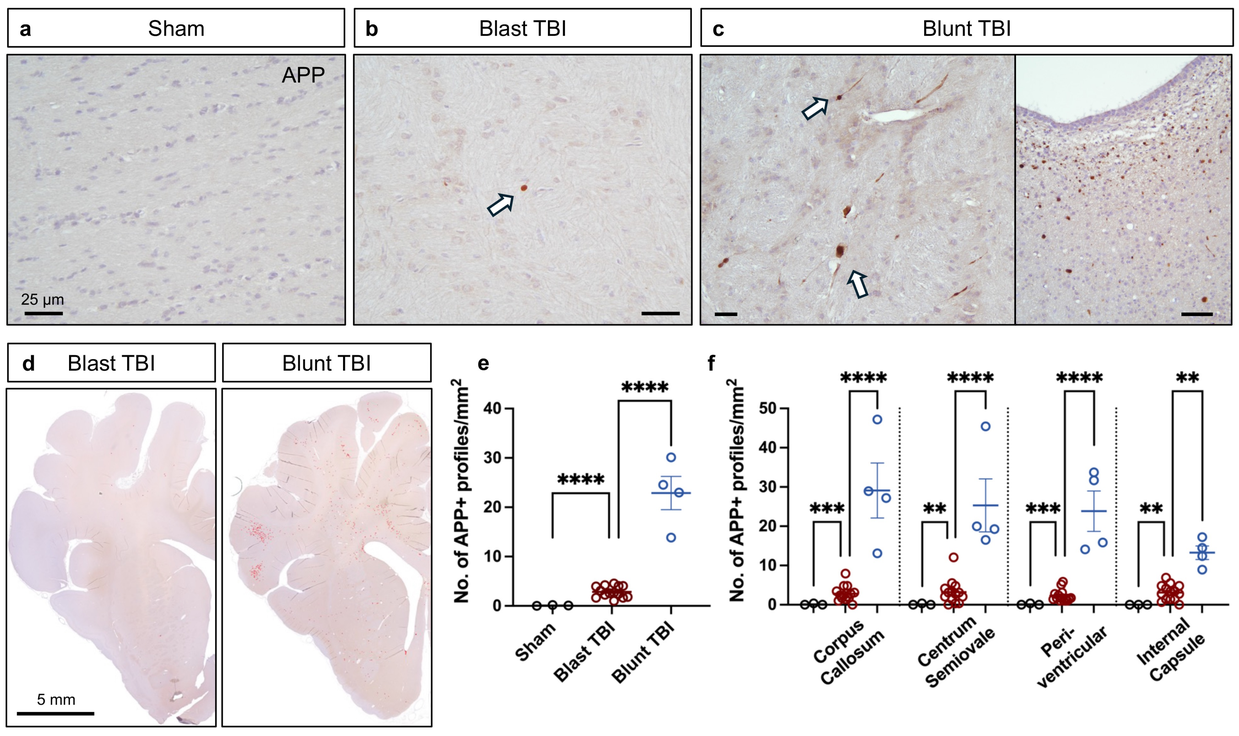
- Immunohistochemistry (IHC): standard FFPE process, followed by HIER, overnight 1° Ab incubation (APP (MAB348) and SNTF (clone 43-8)), 2° Ab incubation, followed by ABC and DAB visualization.

Conclusions and Contributions



Results

Experimental primary blast TBI results in limited APP+ axonal pathology, in contrast to greater numbers of swollen axonal profiles after non-blast rotational acceleration TBI



Extensive SNTF+ axonal degeneration as a signature of DAI following primary blast TBI