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Pre-injury intervention with SV2A-ligand antiseizure drug prevents injury-induced changes in memory performance after traumatic brain injury in rats

Traumatic brain injury (TBI) is a leading cause of disability worldwide, with an estimated global incidence of 27–69 million cases annually. Two major pathological sequelae of TBI are cognitive dysfunction and posttraumatic epileptogenesis (PTE). Our past electrophysiological, behavioral, and biochemical studies suggested that timely post-injury administration of the SV2A ligand antiseizure drugs (ASDs), levetiracetam (LEV) or brivaracetam (BRV), prevents PTE following controlled cortical impact (CCI) injury. This effect was marked by reduced stimulus-evoked and spontaneous epileptiform activity, and prevention of increased seizure susceptibility and hippocampal GluR1/GluR2 ratio elevation. In this pilot study, we tested whether prophylactic administration of BRV (0.21 – 21.0 mg/kg) provides neuroprotection against injury-induced deficits in cognitive function. Rats (postnatal days 25–36) underwent severe CCI trauma (2.0 mm depth) and were randomly assigned to receive a single dose of either BRV (IP) or the saline vehicle at 15–20 minutes before injury. Uninjured controls (sham) did not undergo CCI. Five to eight weeks post-injury, rats completed a four-day active place avoidance test (APA), consisting of one priming day, two training days, and retention test on the last day. Cognitive performance was assessed using four metrics: time to first shock-zone entry, number of shock-zone entries, percentage of time spent in the shock zone, and maximum shock-zone avoidance time. Sham-injured rats outperformed CCI-saline rats across all metrics, confirming cognitive impairment. However, CCI-BRV rats showed significantly better performance than CCI-saline rats, reaching levels equivalent to sham controls. These findings suggest that pre-injury BRV administration provides neuroprotection against TBI-induced cognitive deficits. This study provides insights into potential neuroprotective effects of SV2A ligand ASDs, contributing to future therapeutic strategies.